

Monocyte trafficking critically contributes to inflammatory and autoimmune disease. For example, in atherosclerosis, monocytes become recruited to inflamed arteries, where they differentiate into macrophages that ultimately become pathogenic lipid-laden foam cells.<sup>3</sup> In rheumatoid arthritis, monocyte trafficking to, and differentiation in, the joints has been suggested to feed the autoimmune cycle by providing a source for the high levels of synovial-fluid DCs that ultimately stimulate tissue-damaging autoreactive effector cells.<sup>4</sup> Importantly, however, contrasting the extensive studies of lymphocyte trafficking and homing, relatively little remains known about the complexities and molecular mechanisms directing monocyte trafficking in vivo during inflammation.

Xu and colleagues designed a study to begin to address this paucity by using a noninvasive in vivo retinal imaging approach in the context of experimental autoimmune uveoretinitis (EAU). Thus, the trafficking of adoptively transferred GFP<sup>+</sup> monocytes through inflamed retinal venules was characterized in the absence and presence of antibodies that block the function of specific leukocyte-trafficcking adhesion molecules. It was found that blockade of CD62-L (L-selectin) or CD44 (the hyaluronan receptor) abrogated monocyte rolling, firm adhesion, and ultimate infiltration into the retina, whereas blockage of PSGL-1 (a ligand for P-, E- and L-selectins) and LFA-1 (receptor of ICAM-1) had either partial or no effect, respectively, on these parameters. The findings are in general agreement with a variety of previous studies in other models.

Strikingly, and somewhat surprisingly, CD62-L and CD44 blockade also lead to a rapid and profound depletion of monocytes from the circulation. These effects were inflammation specific, as they were observed in the setting of EAU but not in healthy control animals. Moreover, these treatments caused monocytes to accumulate in specific lymphoid

tissues, with CD44 blockade causing concomitant retention in the lymph nodes and depletion from the spleen, and CD62-L blockade causing accumulation in the spleen and depletion from lymph nodes. Interestingly, these effects were also systemic, as monocyte sequestration (with CD44 blockade) was observed in distant, as well as draining, cervical lymph nodes. From these results, it was concluded that mechanisms controlling monocyte recirculation through peripheral and lymphoid tissues alter in a systemic fashion during inflammation, and that under such conditions, CD62-L and CD44 play important roles in maintaining monocytes within circulation.

This study provides a novel hypothesis and provocative findings. Several of these observations were unexpected and remain unexplained. For example, the observations with CD44 demonstrate a novel and clearly important role for CD44 in monocyte trafficking during inflammation, but the mechanisms driving their reduction in the spleen are unclear. Similarly, how CD62-L blockade drives monocyte accumulation in spleen in the setting of EAU but not in control mice remains mysterious. Such issues suggest a previously unappreciated complexity in the mechanisms and regulation of monocyte trafficking. Thus, in addition to providing new insights, the work by Xu et al provides interesting new questions for future studies.

*Conflict-of-interest disclosure:* The author declares no competing financial interests. ■

## REFERENCES

1. Geissmann F, Jung S, Littman DR. Blood monocytes consist of two principal subsets with distinct migratory properties. *Immunity*. 2003;19:71-82.
2. Palframan RT, Jung S, Cheng G, et al. Inflammatory chemokine transport and presentation in HEV: a remote control mechanism for monocyte recruitment to lymph nodes in inflamed tissues. *J Exp Med*. 2001;194:1361-1373.
3. Ross R. Atherosclerosis—an inflammatory disease. *N Engl J Med*. 1999;340:115-126.
4. Cavanagh LL, von Andrian UH. Travellers in many guises: the origins and destinations of dendritic cells. *Immunol Cell Biol*. 2002;80:448-462.

Rethi and colleagues have shown that Fas, increasingly expressed during T-cell depletion in lymphopenic conditions such as HIV-1 infection, and known to transmit apoptotic (death) signals to repeatedly activated antigen-specific T cells, also plays a role in stimulating T-cell expansion through costimulatory signals in suboptimally activated T cells. They also found that the cytokine IL-7, which is elevated in response to T-cell depletion, increases the efficacy of Fas in inducing proliferation of these cells. In other words, while letting overactivated cells die, the same molecules allow suboptimally activated cells to live and expand, reiterating the process of life and death of the immune system endlessly.

These findings add another piece to the puzzle of HIV pathogenesis, and fit within the current, prevailing interpretation that prolonged immune overactivation induced by HIV during the course of chronic infection exhausts the immune system and leads to AIDS. Initially, it was shown that chronic high levels of immune activation accompany pathogenic HIV/simian immunodeficiency virus (SIV) infection, and the consequent induction of apoptosis during continued, chronic activation of the immune system deletes reactive T cells, resulting in progression to AIDS.<sup>1,2</sup> This concept was supported by the finding that apoptosis does not mainly occur in HIV-infected cells as first suspected, but rather in bystander cells that are not infected by the virus.<sup>3</sup> The increased susceptibility of these bystander cells to apoptosis was shown to correlate with disease progression,<sup>4</sup> leading to the conclusion that chronic activation of the immune system is the primary mechanism for cell depletion. The immune system is eventually exhausted by long-term HIV-1 infection.<sup>5</sup> This explains why markers of T-cell activation are more closely associated with disease progression than is plasma viral load during HIV infection,<sup>6</sup> and CD4 T-cell depletion correlates more closely with levels of immune activation than with viral load during both HIV-1 and HIV-2 infection.<sup>7</sup> The nonhuman primate model provided the most elegant, although indirect, evidence that chronic hyperactivation of the immune system is key to HIV disease progression and AIDS: despite persistently high viral loads and massive initial loss of CD4 memory T cells in the *lamina propria* of the gut, SIV infection in sooty mangabeys is not pathogenic, but rather is characterized by

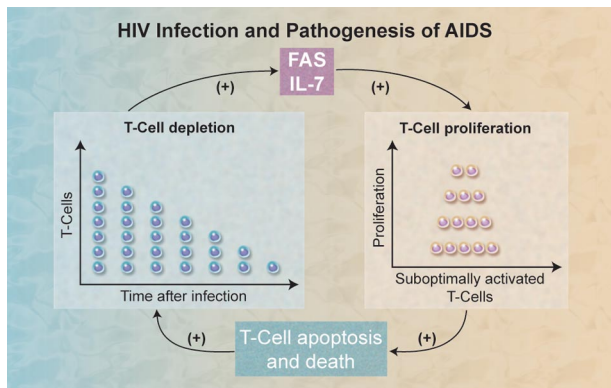
## ● ● ● IMMUNOBIOLOGY

Comment on Rethi et al, page 1195

# Fas, IL-7, and T cells: live and let die

Franco Lori VIROSTATICS

In the context of HIV-driven, prolonged overactivation of the immune system, ultimately leading to AIDS, Rethi and colleagues have identified key components able to support both life and death of immune-competent T cells.



HIV infection is characterized by progressive T-cell depletion. T-cell depletion increases the production of both apoptosis stimulating fragment (FAS) and interleukin-7 (IL-7). As shown by Rethi et al, IL-7 synergizes with FAS to induce proliferation of suboptimally activated T cells. It is known that chronic hyperactivation/proliferation induces T-cell apoptosis and death, particularly of bystander cells. The whole process results in T-cell depletion, thus completing the HIV-AIDS pathogenesis cycle. Professional illustration by Alice Y. Chen.

limited immune activation and low bystander immunopathology.<sup>8</sup> This is in stark contrast to rhesus macaques, in which persistent SIV replication and resultant high viral loads are associated with high levels of immune activation and progression to AIDS. The reduced response by the sooty mangabey immune system to chronic immune stimulation explains the lack of pathogenic effects despite high viral loads similar to those seen in infected macaques.<sup>9</sup>

The findings of Rethi and colleagues improve upon the current knowledge of hyperactivation-mediated immune deficiency: while previous literature mainly explains how immune hyperactivation induces immune deficiency, the present manuscript addresses the question of how immune deficiency (or at least one aspect of it, T-cell depletion) leads to hyperactivation, by rendering a subset of T cells more prone to proliferation. The complex interplay between hyperactivation and resultant immune deficiency and, now, between immune defi-

ciency and immune hyperactivation, is becoming increasingly clear, completing the vicious cycle that leads from HIV infection to AIDS.

*Conflict-of-interest disclosure: The author declares no competing financial interests.* ■

## REFERENCES

1. Ameisen JC, Capron A. Cell dysfunction and depletion in AIDS: the programmed cell death hypothesis. *Immunol Today*. 1991;12:102-105.
2. Meyaard L, Otto SA, Jonker RR, et al. Programmed death of T cells in HIV-1 infection. *Science*. 1992;257:217-219.
3. Finkel TH, Tudor-Williams G, Banda NK, et al. Apoptosis occurs predominantly in bystander cells and not in productively infected cells of HIV- and SIV-infected lymph nodes. *Nat Med*. 1995;1:129-134.
4. Gougeon ML, Lecoq H, Dulioust A, et al. Programmed cell death in peripheral lymphocytes from HIV-infected persons: increased susceptibility to apoptosis of CD4 and CD8 T cells correlates with lymphocyte activation and with disease progression. *J Immunol*. 1996;156:3509-3520.
5. Zinkernagel RM, Hengartner H. T-cell-mediated immunopathology versus direct cytolysis by virus: implications for HIV and AIDS. *Immunol Today* 1994;15:262-268.
6. Giorgi JV, Hultin LE, McKeating JA, et al. Shorter survival in advanced human immunodeficiency virus type 1 infection is more closely associated with T lymphocyte activation than with plasma virus burden or virus chemokine coreceptor usage. *J Infect Dis*. 1999;179:859-870.
7. Sousa AE, Carneiro J, Meier-Schellersheim M, et al. CD4 T cell depletion is linked directly to immune activation in the pathogenesis of HIV-1 and HIV-2 but only indirectly to the viral load. *J Immunol*. 2002;169:3400-3406.
8. Gordon SN, Klatt NR, Bosinger SE, et al. Severe depletion of mucosal CD4+ T cells in AIDS-free simian immunodeficiency virus-infected sooty mangabeys. *J Immunol*. 2007;179:3026-3034.
9. Silvestri G, Sodora DL, Koup RA, et al. Nonpathogenic SIV infection of sooty mangabeys is characterized by limited bystander immunopathology despite chronic high-level viremia. *Immunity*. 2003;18:441-452.

## ● ● ● RED CELLS

Comment on Yamashita et al, page 1482

# Erythropoiesis—once more HIF!

Joachim Fandrey UNIVERSITÄT DUISBURG-ESSEN INSTITUT FÜR PHYSIOLOGIE

In this issue of *Blood*, Yamashita and colleagues provide evidence for additional oxygen-dependent regulation of erythropoiesis through HIF-2 $\alpha$ -controlled expression of vascular adhesion molecule-1 in endothelial cells of the bone marrow microenvironment.

Oxygen-dependent regulation of erythropoiesis by hypoxia-inducible production of erythropoietin (EPO) has stimulated research for decades. It has ultimately led to the identification of cellular oxygen sensors in control of EPO production.<sup>1</sup> Hypoxia-inducible transcription factor-1 (HIF-1) was identified by Wang et al from hypoxia-induced binding of a transcription factor complex to the EPO enhancer.<sup>2</sup> Dissecting the regulatory pathways back to the cellular O<sub>2</sub> sensors revealed a HIF-1 dimer consisting of an oxygen-labile  $\alpha$ -subunit (HIF-1 $\alpha$ , -2 $\alpha$ , and -3 $\alpha$ ) and a constitutive  $\beta$ -subunit. Although HIF-1 $\alpha$  was initially thought to control EPO gene expression, recent studies indicate a dominant role for HIF-2 $\alpha$  in regulating EPO synthesis in mice<sup>3,4</sup> and also in humans.<sup>5</sup>

In this issue of *Blood*, Yamashita and colleagues report on their use of mice with a knock-down mutation in HIF-2 $\alpha$  that presented with normocytic anemia. Interestingly, EPO protein levels in HIF-2 $\alpha$  knockdown mice were unaffected and obviously not responsible for causing the anemia. Instead, the authors identified a major defect in the hematopoietic microenvironment of HIF-2 $\alpha$  knockdown mice that was due to reduced endothelial-specific expression of vascular adhesion molecule-1 (VCAM-1). VCAM-1 supports the interaction of hematopoietic and endothelial cells in the bone marrow microenvironment and is required for maturation of erythroid cells. Hypoxia-inducible VCAM expression was selectively regulated by HIF-2 $\alpha$ , and defective erythropoiesis was rescued in HIF-2 $\alpha$  knock-down mice with selectively restored HIF-2 $\alpha$  expression in endothelial cells. As such, the study by Yamashita and colleagues underscores the importance of HIF-2 $\alpha$  in the O<sub>2</sub>-dependent regulation of erythropoiesis. This work adds a further piece to the puzzle of how low oxygen tension in the bone marrow supports hematopoiesis by facilitating the interaction of stromal and hematopoietic cells.

Unexpected and puzzling, however, is the fact that HIF-2 $\alpha$  knock-down did not reduce EPO synthesis; on the contrary, hepatic EPO mRNA levels in the knock-down mice tended to be higher than in wild-type controls. This finding deserves further study. However, the effect of reduced HIF-2 $\alpha$  expression on the hematopoietic microenvironment, but not EPO synthesis, may indicate that remaining levels of HIF-2 $\alpha$  in knock-down animals with