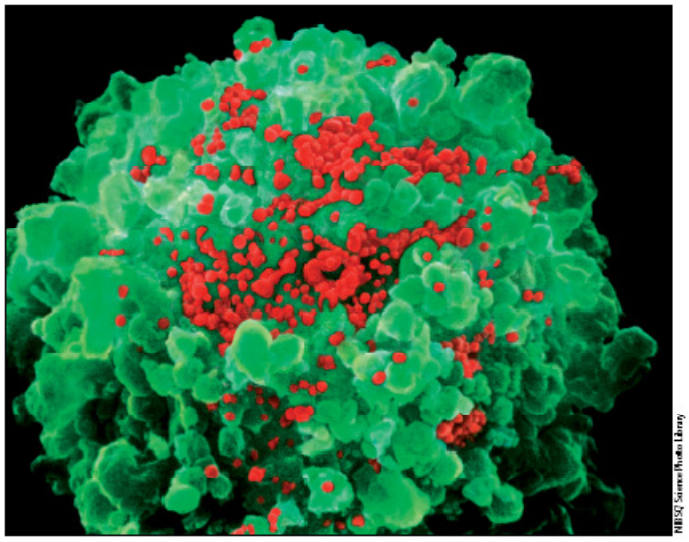
Lymph nodes and pathogenesis of infection with HIV-1

Lymphadenopathy was identified as an essential feature of AIDS soon after its appearance and before the identification of HIV as its cause.[1] However, lymphadenopathy has not subsequently received much attention. Recently, two studies have allowed lymph nodes to regain centre stage.

Elizabeth Nies-Kraske and colleagues[2] studied four patients with a history of striking CD4-T-cell decline (from a median of 719 cells per μL to 227 cells per μL) despite fully suppressive antiretroviral therapy over a period of 18–24 months. They found that the only common findings in all of the patients were collagen deposition and compromised lymphoid tissue architecture, particularly in the paracortical-T-cell zone. This zone supports naive T cells that have migrated from the thymus, supplies memory-CD4-T cells, and is important for T-cell maturation. Di Mascio and colleagues[3] used a non-depleting humanised anti-CD4 monoclonal antibody labelled with indium-111 to visualise the CD4-T-cell pool in vivo in rhesus macaques infected with simian immunodeficiency virus. Extrapolating the data, they estimated that the total number of lymphocytes in adult human beings is between $1{\cdot}9\times10^{12}$ and $2{\cdot}9\times10^{12}$ cells (five–ten-fold higher than previously estimated); moreover, peripheral blood seems to contain only 0·3–0·5% of lymphocytes with respect to lymphoid tissue, and, at most, the gut contains a number of CD4 T cells equal to that of the spleen (ie, no more than 15% of the total pool).[3]

How do these results improve our knowledge of HIV pathogenesis? Secondary lymphoid organs and tissues (that include lymph nodes, spleen, and various mucosal-associated lymphoid tissue such as gut-associated lymphoid tissue) play a critical part in antigen presentation to mature lymphocytes, and their structure



NIBSC/Science Photo Library

Lymph nodes contain the majority of T cells (green), making them crucial in the pathogenesis of HIV (red)

is essential to this function. Although the role of the gut has been emphasised in recent years, the work of Di Mascio and colleagues showing that lymph nodes contain 70% of total CD4 T lymphocytes in the body highlights their crucial role in AIDS pathogenesis.

In patients infected with HIV, lymph nodes are highly inflamed, with heightened expression of adhesion molecules, cytokine dysregulation, and lymphocyte sequestration of activated effector lymphocytes excessively attracted or retained in lymphoid tissue.[4]

In this context, lymph node structure is progressively remodelled and finally destroyed. In early stages of infection, the high endothelial venules begin to accumulate abnormal levels of collagen, and the process of fibrosis spreads from there throughout the T-cell zone,[5] making nodes increasingly fibrotic, smaller in size, and substantially depleted of lymphocytes.[6]

Lymph node fibrosis has serious consequences, since the magnitude of fibrosis predicts (inversely) the amount of CD4-T-cell restoration in peripheral blood among people starting antiretroviral therapy,[7] and can allow continuing CD4-T-cell loss despite full suppression of HIV RNA in the blood.[2]

To consider how fibrosis might be prevented or treated, we must first ask why CD4 T cells are attracted to lymph nodes during infection with HIV-1. Recent data[8] show that the HIV-surface glycoprotein gp120 might have a major role in attracting both infected and uninfected CD4 lymphocytes to lymph nodes, where infection with HIV-1 induces the expression of activation markers both on infected and on the uninfected bystander T cells, creating new cell targets for HIV-1. A combination of infection with HIV-1 and activation then drives cells into apoptosis.[3]

What are the possible causes of fibrosis? In rhesus macaques infected with simian immunodeficiency virus the deposition of collagen type I starts in the lymphatic vessels as early as 7 days following infection, and coincides with increased immune activation and increased frequencies of transforming growth factor β1 (TGF-β1) positive regulatory T cells in the T-cell zone of lymph nodes.[10] Therefore, fibrosis in these animals could be due to TGF-β1 overexpression. Interestingly, sooty mangabeys, who do not progress to AIDS, have lower amounts of collagen deposition in lymph nodes, compared with rhesus macaques that are infected.[10] TGF-β1-positive regulatory T cells have profibrotic effects in vitro on human fibroblasts derived from lymphatic tissue,[10] so this mechanism might also be active in human beings.

New approaches to treatment can be tried on the basis of the results of these studies. Antifibrotic drugs such as relaxin (or perhaps drugs inhibiting TGF-β signalling) might be tested to limit depletion and improve CD4-T-cell reconstitution during antiretroviral therapy.[5,10] Alternatively or additionally, neutralisation of gp120 bioactivity might prolong normal T-cell trafficking and limit CD4-T-cell depletion.[8]

*Francesca Cainelli, Alfredo Vallone, Matthew N Tanko, *Sandro Vento*

Departments of Internal Medicine (FC, SV) and Pathology (MNT), School of Medicine, Faculty of Health Sciences, University of Botswana, Gaborone, Botswana; and Infectious Diseases Unit, Annunziata Hospital, Cosenza, Italy (AV)

ventosandro@yahoo.it

We declare that we have no conflicts of interest.

1 Metroka CE, Cunningham-Rundles S, Pollack MS, et al. Generalized lymphadenopathy in homosexual men. *Ann Intern Med* 1983; 99: 585–91.

2 Nies-Kraske E, Schacker TW, Condoluci D, et al. Evaluation of the pathogenesis of decreasing CD4+ T cell counts in human immunodeficiency virus type 1-infected patients receiving successfully suppressive antiretroviral therapy. *J Infect Dis* 2009; 199: 1648–56.

3 Di Mascio M, Paik CH, Carrasquillo JA, et al. Noninvasive in vivo imaging of CD4 cells in simian-human immunodeficiency virus (SHIV)-infected nonhuman primates. *Blood* 2009; 114: 328–37.

4 Biancotto A, Grivel JC, Iglehart SJ, et al. Abnormal activation and cytokine spectra in lymph nodes of people chronically infected with HIV-1. *Blood* 2007; 109: 4272–79.

5 Schacker T. The role of secondary lymphatic tissue in immune deficiency of HIV infection. *AIDS* 2008; 22 (suppl 3): S13–18.

6 Biberfeld P, Ost A, Porwit A, et al. Histopathology and immunohistology of HTLV-III/LAV related lymphadenopathy and AIDS. *Acta Pathol Microbiol Immunol Scand A* 1987; 95: 47–65.

7 Schacker TW, Reilly C, Beilman GJ, et al. Amount of lymphatic tissue fibrosis in HIV infection predicts magnitude of HAART-associated change in peripheral CD4 cell count. *AIDS* 2005; 19: 2169–71.

8 Green DS, Center DM, Cruikshank WW. Human immunodeficiency virus type 1 gp120 reprogramming of CD4+ T-cell migration provides a mechanism for lymphadenopathy. *J Virol* 2009; 83: 57 65–72.

9 Biancotto A, Iglehart SJ, Vanpouille C, et al. HIV-1-induced activation of CD4+ T cells creates new targets for HIV-1 infection in human lymphoid tissue ex vivo. *Blood* 2008; 111: 699–704.

10 Estes JD, Wietgrefe S, Schacker T, et al. Simian immunodeficiency virus-induced lymphatic tissue fibrosis is mediated by transforming growth factor β1-positive regulatory T cells and begins in early infection. *J Infect Dis* 2007; 195: 551–61.