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. However, lymphadenopathy has not subsequently received much attention. Recently, two studies have allowed lymph nodes to regain centre stage.

Elizabeth Niew-Kraske and colleagues 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 naïve T cells that have migrated from the thymus, supplies memory-CD4 T cells, and is important for T-cell maturation. Di Mascio and colleagues 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 1.9×10^{11} and 2.6×10^{12} cells (five-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).

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 therefore in the development of immunity to HIV.
is essential to this function. Although the role of the gut has been emphasized in recent years, the work of Di Maio and colleagues showing that lymph nodes contain 70% of total CD4 T lymphocytes in the body highlights their crucial role in immune function.

In patients infected with HIV, lymph node structures are highly inflamed, with heightened expression of adhesion molecules, cytokine dysregulation, and lymphocyte sequestration of activated effector lymphocytes excessively attracted or retained in lymphoid tissues.

In this context, lymph node structures are 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, making nodes increasingly fibrotic, smaller in size, and substantially depleted of lymphocytes.

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; and can allow continuing CD4 T-cell loss despite full suppression of HIV RNA in the blood.

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. Recent data 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 cells, creating new cell targets for HIV-1. A combination of infection with HIV-1 and activation then drives cells into apoptosis.

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 (TGF-β1) positive regulatory T cells in the T-cell zone of lymph nodes. 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. TGF-β1-positive regulatory T cells have profibrotic effects in vitro on human fibroblasts derived from lymphatic tissue in culture; 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. Anti-fibrotic drugs such as relaxin (or perhaps drugs inhibiting TGF-β signalling) might be tested to limit depletion of CD4 T cells in HIV patients infected with HIV-1.

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We declare that we have no conflicts of interest.

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