Seminars in Immunology 20 (2008) 187–195

Contents lists available at ScienceDirect

Seminars in Immunology

journal homepage: www.elsevier.com/locate/ysmim

Review

The lymph node in HIV pathogenesis

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ARTICLE INFO

Keywords:
CD38
Cell cycle
HIV
Immune activation
Lymph Node
Microbial Translocation
Toll like receptors

ABSTRACT

Since the earliest days of the AIDS epidemic, clinicians and researchers have recognized the importance of lymphoid tissue both in the clinical manifestations of disease and in its pathogenesis. Generalized lymphadenopathy was one of the earliest harbingers of AIDS in the United States and over the past 27 years an increasing body of evidence has implicated the lymphoid organs as central to the pathogenesis of immune deficiency in chronic HIV-1 infection. In this essay, we will review some of the data that have been accumulated and propose a testable model that may reconcile them.

1. Philosophy of the lymph node

Neither Aristotle nor Socrates gave much thought to lymph nodes as seats of knowledge or emotion, probably because they were unaware of them as their first description was attributed to Gaspare Aselli (1581–1626), a professor at the University of Padova. But Aselli confused the role of the lymph node, naming it "the pancreas of Aselli". This confusion was later corrected and now both meta-immunologists and real ones attribute a central role in human development to the lymph nodes as critical elements for immune homeostasis. Our understanding of their function in health and disease is still evolving.

What we know is that lymph nodes provide a structural background to support complex interactions among various cell types (dendritic cells, B and T lymphocytes, etc.) involved in building an immune response to an invading pathogen; this response results in generation of an adaptive immune response by helper T cells, cytotoxic T lymphocytes (CTL), antibody-producing plasma cells, or all three. The critical importance of the tissue cytoarchitecture is underscored by the inability of the mixture of isolated lymphocytes to build an efficient humoral response *in vitro* that depends on cell density, culture vessel geometry, agitation, oxygenation and other factors [1], whereas isolated blocks of structurally preserved lymph nodes readily produce antibodies when challenged *in vitro* by antigen [2].

Defined by the expression of homing receptors for lymphoid tissue, both naïve and central memory T cells are characteristically selectively retained in lymph nodes as they circulate. Signals needed for homeostatic proliferation of these cells are provided there by homeostatic cytokines such as interleukin-7. Professional antigen-presenting cells such as dendritic cells also accumulate in lymph nodes, where they present exogenous microbial antigens for priming and expansion of adaptive immune responses. Thus, naïve T cell maturation is directed in these sites, and anamnestic expansion of central memory cells in response to recall antigens is also initiated there. These events are carefully orchestrated. Cells are not moving through the lymph nodes stochastically but rather often follow roads or 'byways' that stromal elements provide for lymphocyte migration. This arrangement ensures that the two partners (antigen-presenting cells and responding lymphocytes) are using the same track and do not miss each other [3]. Recognition of peptide/MHC on APC surfaces by rare T cell receptors is stabilized by interactions of accessory molecules and their ligands on T cells and APC. Bidirectional cross-talk as a result of these interactions results in timed expression of additional costimulatory molecules as well as the elaboration of cytokines, that in their turn, contribute to orderly intercellular interactions. Also, upon receptor binding, cytokines regulate APC maturation as well as T cell and B cell maturation and expansion. Thus, an adaptive immune response is built via highly orchestrated intercellular interactions coupled with the release of appropriate cytokines that bind to cell receptors and promote orderly maturation of their targets. Upon exposure to a new antigen in the setting of a healthy lymph node, rare naïve CD8+ T cells that can recognize a microbial peptide will mature to develop effector function and with sufficient expansion, can provide a host response of sufficient magnitude to promote clearance of the pathogen. Concurrently, expansion of naïve CD4 T cells may provide a source of helper cytokines to facilitate antimicrobial defenses and the cytokine environment at the time of naïve CD4+ T cell maturation may direct the character of the effector cell

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doi:10.1016/j.smim.2008.06.001

expansion such that the memory/effector progeny of this expansion may be characterized as having a predominantly Th1, Th2, Th17, or T-reg phenotype with relatively distinct patterns or cytokine expression upon restimulation [4]. A fraction of these cells will develop a central memory (CM) phenotype that will persist in lymphoid tissues after antigen clearance in order to allow re-expansion of effector cells should the same antigen be presented systemically.

Importantly, effector T cells, which, in this conceit are full of cytokines and cytolytic molecules, are characteristically not encouraged to stay very long in lymphoid tissues. Indeed, having these readily activated, cytokine-producing cells around might result in the death of critical antigen-presenting cells or could induce dysregulated responses by naïve and memory cells that are exquisitely sensitive to these cytokine signals. Thus, the homing molecules of effector cells typically direct them to tissue sites where they are needed to destroy or contain invading pathogens and to persuade other cells to do the same. This is how it is supposed to work.

2. Impairment in adaptive defenses in HIV-1 infection and the function of the HIV-1 infected lymph node

In HIV-1 infection, the function of the lymph node is disrupted. From a holistic perspective, both cellular and humoral immune responses are dramatically impaired in HIV infection. To start, in most infected persons, there is progressive depletion of circulating CD4+ T cells. Also, the opportunistic infections that complicate HIV-1 infection and that define AIDS reflect profound impairments in cellular (as well as humoral) immune responses. The ability of HIV-infected persons to develop strong T cell and B cell responses to immunization with neoantigens and to recall antigens is often dramatically impaired [5–7]. This impairment reflects the profoundly weakened ability of the infected host to expand naïve T cells and to expand functional memory cells. Whether this is a simple consequence of T cell depletion or is related to impairments in their functional capacities remains to be completely resolved, but at the very least, there is clear evidence that naïve T cell expansion is compromised in chronic HIV infection [8–10]. Also, among circulating T cells, *in vitro* expansion in response to recall antigens by both CD4+ and CD8+ T cells is diminished [11–14]. While some of the latter defect might be related to diminished numbers of antigen-reactive memory cells, even on a single-cell basis, the ability to express single or multiple cytokines is impaired [15,16].

So the HIV-infected lymph node may not be doing its job. Why? Well, it's a mess! From the earliest days of the AIDS epidemic, lymph node pathology was a defining characteristic of infection [17,18]. Acute HIV infection is often associated with generalized lymph node enlargement [19,20], and with time, it may be found in most patients if looked for carefully [20]. In early stages of infection, these nodes are characterized histopathologically by pronounced follicular hyperplasia that, as disease advances, may evolve into a pattern of follicular involution [18]. It seems that HIV replication somehow triggers lymphoid enlargement as after HIV replication is suppressed with application of antiretroviral therapies, lymph node enlargement, when present, tends to diminish dramatically [21]. One might suspect that in the HIV-infected lymph node, cells interact with each other in a less orderly way, although exact descriptions of intercellular interactions in situ have not yet been performed. More data are available regarding perturbations of cytokine expression in HIV-infected lymph nodes. This perturbation was demonstrated both in single-cell assays [22] and in tissue histoculture experiments [23]. There was dramatic alteration in the normal pattern of constitutive cytokine expression, with some cytokines such as interleukin-1B, interleukin-2, interferon γ, and interleukin-15 characteristically found in increased concentrations and some others such as MIP-1α and SDF-1β substantially diminished. Collagen deposition and fibrosis are increasingly recognized in these nodes and these findings are actually demonstrable even in the earliest stages of infection [24]. As untreated infection progresses and as circulating CD4 T lymphopenia becomes more pronounced, nodes become increasingly fibrotic and smaller in size. Interestingly and not surprisingly, among persons who start antiretroviral therapies, the magnitude of fibrosis predicts inversely the magnitude of CD4 T cell restoration in peripheral blood [25]. Persons with advanced HIV infection and AIDS often have lymph nodes that are characteristically small, fibrotic, and profoundly depleted of lymphocyte populations [26].

Why does this happen in HIV infection but not with most all other viral diseases? This phenomenon may be related to the nature of the pathogen. HIV is one of a handful of recognized pathogens that are capable of (and actually enjoy) replication in immunologic organs. Thus, in this case, HIV antigens accumulate in lymphoid tissue in concentrations far exceeding those observed for most other microbial pathogens, which localize and replicate predominantly at the other sites. This excessive accumulation of HIV antigens is the result of the efficient replication of virus in (activated) T cells and of the persistence of viral particles on follicular-dendritic cells [27]. Viral accumulation in lymphoid tissues may be enhanced by the ingestion of dying HIV-infected cells by nearby APC and may serve as a reservoir for new infections. All these events, which occur within the lymph nodes can result in an explosive concentration of foreign antigen that is not ordinarily encountered in lymphoid tissues except in occasional circumstances (see below). On the other hand, are high concentrations of antigen in lymphoid tissues sufficient to explain the pathogenesis of HIV infection? Perhaps, but it should be recognized that circulating levels of other viral pathogens that cause chronic disease (e.g. hepatitis B virus) typically exceed those of HIV by two to three logs or more [28], yet these circulating levels of viral antigen do not result in profound immune deficiency or even in the generalized lymph node enlargement that is typical of HIV infection.

These explosive antigen concentrations apparently present a challenge for HIV-reactive effector/memory T cells: their homing molecules direct them to the tissues where most pathogens invade, but, unlike the case for most other pathogens, there are also unusually high concentrations of microbial (HIV) antigen in lymph nodes. Perhaps the high concentration of viral antigens in lymphoid tissues promotes an excessive accumulation of HIV-reactive effector memory cells in these lymphoid sites [29–32] sites from which effector memory cells are typically excluded. We propose that TCR triggering at these sites results in significant cytolysis of infected cells (although one team found a relative exclusion of HIV-reactive CTL from follicular sites within the lymph node where HIV-infected cells were concentrated [32]) and also in a dysregulated inflammatory cytokine environment [22,23,33,34] that wreaks some havoc on the normally immunologically ordered environment of the lymph node. As noted above, a number of proinflammatory cytokines were found to be elevated in the HIV-infected lymph node: most consistently, interleukins-1β, 2, 12, and 15 and interferon γ. These derangements have likely consequences on the maturation of both primary and anamnestic responses in HIV infection.

Is this situation unique to HIV infection? Surely other pathogens that can be responsible for definitive clinical syndromes also can propagate in lymphoid tissue. As examples, Epstein–Barr virus (EBV), measles virus, and Mycobacterium tuberculosis will replicate in lymphoid tissues. Interestingly, these infections are also associated with evidence of profound perturbations of immunity