Published in final edited form as:
Semin Immunol. 2008 June ; 20(3): 187–195. doi:10.1016/j.smim.2008.06.001.

THE LYMPH NODE IN HIV PATHOGENESIS

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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.

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

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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 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.

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 is 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 2–3 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 that include global anergy in the setting of turberculosis [35] or acute measles virus infection [36,37]. There is also evidence of transient impairment of skin test reactivity in acute EBV infection [38,39], which is characteristically self-limited as viral replication is ultimately controlled by an effective host antiviral immune response [40] that is lacking in HIV-1 infection. Thus we propose that microbial infection in lymphoid tissues sets the stage for derangements in cellular immunity that in HIV-1 infection are persistent and progressive.

Immune Activation and the Pathogenesis of Immune Deficiency in chronic HIV infection

Despite profound immune deficiency in HIV-1 infection, immune activation is recognized as characteristic [41–45]. Although precise definitions of immune activation are lacking and different authors mean different things when using this term, it is clear that there is broad hyperactivation of immune cells and heightened levels of a variety of immune cytokines in chronic HIV-1 infection. As examples, there are polyclonal increases in immunoglobulins reflective of B cell activation [43], increased circulating levels of a variety of cytokines such as interleukin-6, and tumor necrosis factor and its receptors [46–48], heightened expression of various activation markers on T lymphocyte populations [49,50] and on antigen presenting cells such as monocytes [51–54] and B lymphocytes [55]. There is increasing evidence that T-cell markers of immune activation (e.g. CD38) predict disease progression better than does the magnitude of plasma viremia [56,57]. While cell surface markers such as CD38 may be good predictors of disease outcome in HIV infection, there is little indication that this surface antigen or other similar markers are actually on the critical path of cell losses and immune deficiency in HIV infection. Rather many of these markers seem to reflect a generalized immune activation state in chronic HIV infection. Distinguishing those activation pathways that actually drive immune deficiency from those simply reflect it is therefore a priority in HIV pathogenesis research.

In non-human primates, chronic simian immunodeficiency virus (SIV) infection causes progressive disease only in the setting of sustained immune activation

The importance of immune activation in the pathogenesis of immune deficiency in HIV-1 infection is supported by studies of infection with a related virus (SIV) in non-human primates. While Asian rhesus macaques that are not natural hosts for SIV develop CD4+ T cell depletion and progressive immune deficiency after SIV infection [58], African monkeys that are natural hosts for SIV such as the sooty mangabey and the African green monkey tolerate high level viremia and rarely experience significant CD4+ T cell losses when infected [59,60]. Apparently, these animals, naturally adapted to SIV have had the opportunity to evolve mechanisms to tolerate viral infection without developing disease [61]. Exactly how they did this is incompletely resolved presently and whether a single pathway or multiple pathways

determine tolerance of infection without immune activation remains to be determined. Importantly, these animals are fully capable of recognizing SIV antigens [61]; thus, low level immune activation in them is not a consequence of "ignorance". Thus, in HIV infection, it is reasonable to propose either that pathways downstream of cognate recognition of HIV peptides are essential for immune activation in this setting or, alternatively, that other mechanisms such as bystander activation are important in driving the immune activation that drives pathogenesis.

Immune activation in chronic HIV infection is associated with increased turnover of both CD4+ and CD8+ T cells and is somehow related to HIV replication

As noted above, circulating lymphocytes in HIV-infected persons express high levels of phenotypic markers of cellular activation and high levels of a variety of cytokines can be found in circulation. Nonetheless, the role of these markers and cytokines in the pathogenesis of immune deficiency is uncertain. Cellular activation is reflected also in an accelerated cellular turnover that can be measured by several techniques. Cells that were activated recently *in vivo* to enter the cell cycle can be detected with flow cytometry by nuclear staining for Ki67 [62] antigen. To detect cells that are in or recently have been in the S (DNA synthesis) phase of the cell cycle, the thymidine analogue BrdU can be administered and its uptake into cellular DNA can be detected by flow cytometry *ex vivo*. [63]. Likewise, *ex vivo* incubation of fresh blood samples with BrdU permits detection by flow cytometry of cells that were recently activated *in vivo* to enter S phase of the cell cycle [45,64]. Cell turnover also can be evaluated by stable isotope mass spectrometry in sorted cell populations after *in vivo* administration of deuterium-containing glucose or water [41]. Using these techniques, one can demonstrate heightened turnover of both CD4+ and CD8+ T cells in peripheral blood [42,45,64,65] and lymphoid tissue [63] of persons with chronic HIV infection. The decreases in T cell activation and turnover in HIV infection after application of suppressive antiretroviral therapies [42,64, 65] make it clear that viral replication must be implicated directly or indirectly in much of this process. Nonetheless, while the two are coordinated, the decay in plasma viremia is much more rapid than the decay in the frequency of CD4+ T cells in S phase [64]. Specifically, the proportion of BrdU+ CD4+ T cells in untreated HIV-infected persons averaged more than 8 fold greater than among HIV seronegative controls. While, in the first 10 weeks of therapy, viral load fell approximately three logs, the fraction of BrdU+ CD4+ T cells decreased less than 40% during this period and with a biphasic decay, even after one year of therapy, the decrease of this fraction was less than 60% and apparently remained greater than that seen among healthy controls. As circulating BrdU+ T cells in HIV infection are primed to die rapidly [66], these disparities are not likely to be a consequence of delayed decay of these cells from circulation. Thus, there is evidence that HIV infection is associated with heightened cellular turnover and death that is at least partially corrected by application of suppressive antiretroviral therapies. This stated, heightened cellular turnover might be a driver of cellular losses, could reflect a homeostatic response to lymphocytopenia, a combination of both or conceivably an epiphenomenon of immune activation that plays no role in the pathogenesis of immune deficiency.

Immune activation does not just reflect a homeostatic response to lymphocytopenia

It is not unreasonable to propose that immune activation in chronic HIV infection is a consequence of lymphocytopenia as CD4+ lymphocyte numbers and ultimately all lymphocyte types in circulation tend to diminish dramatically [50,67]. There is also a significant inverse relationship between circulating CD4+ T cell counts and plasma levels of an important homeostatic cytokine – interleukin-7 [68,69]. Nonetheless, we do not think that the heightened

T cell activation and turnover in chronic HIV infection reflect to any large degree a homeostatic responses to lymphocytopenia as the frequency of circulating S phase cells is not related to circulating CD4 T cell numbers, total T cell numbers or total lymphocyte numbers [45,64]. Moreover, although as noted above, the decreases in immune activation and cellular turnover are more rapid than decays in plasma viremia, the decreases in circulating S phase T cells and decreases in cellular turnover are seen very soon after suppression of HIV replication and long before lymphocyte numbers even tend to normalize [64,70,71]. These data suggest that homeostatic expansion in response to lymphocytopenia is not a major contributor to the immune activation and cellular turnover of chronic HIV-1 infection.

Immune activation and T cell turnover in chronic HIV infection appear to be driven by bystander mechanisms rather than through cognate peptide recognition

If a homeostatic drive to restore lymphocyte numbers is not the major determinant of immune activation in chronic HIV infection, what then are the plausible drivers of cellular activation and turnover in this chronic infection? While the magnitude of HIV viremia correlates with the frequency of cells in cycle [45,72] it is difficult to ascribe the broad T cell activation in chronic HIV infection as an expansion and activation response to HIV antigens, as only a minority of the activated T cells in chronic HIV infection can be shown to be HIV-reactive [45,73] and we have found that the circulating S phase (BrdU+) T cells in chronic HIV infection only rarely show evidence of recent TCR engagement [45]. Specifically, although these S phase cells all express the activation marker CD38, they do not express CD25 (the IL-2 receptor alpha chain) or the C-type lectin CD69 that are both typically upregulated after cellular activation through binding of the T cell receptor by peptide antigen. More specifically, circulating S phase CD8+ T cells rarely bind HIV peptide/HLA tetramer complexes [45]. Thus, mechanisms other than those due to recognition of HIV antigens- or other cognate peptide driven activation processes likely underlie the heightened immune activation that characterizes HIV infection.

Activation and turnover of central memory T cells is central to the pathogenesis of chronic HIV infection in humans and SIV infection in rhesus macaques

As noted above, T cells can be divided broadly according to their maturation status into “naïve”, “central memory” and “effector memory” cells [74]. The T cell receptor (TCR) diversity of naïve T cells represents the full spectrum of TCR gene rearrangements that have occurred within the thymus and have matured therein. These recombination events and selection during thymic maturation result in emergence of naïve T cells with receptors with intermediate affinity for self HLA antigens expressing endogenous peptides within. Naïve T cells with high affinity for self have been deleted to avoid autoimmunity while T cells with low affinity fail to mature and exit from thymic tissues and this is good because they will not likely bind sufficiently well to self HLA, even self HLA containing exogenous peptides derived from invading microbes. After the first encounter with antigen in lymphoid tissues, naïve T cells will mature to cells with effector (cytokine expression, and cytolytic) function in order to facilitate defense against and clearance of invading microbes. As noted earlier, effector memory cells mature to express homing receptors that direct their distribution to tissue sites where microbial invasion is expected. Among those cells that have matured in response to neoanitgen exposure, some develop a central memory phenotype. Central memory cells express homing receptors for lymphoid tissue where they reside, waiting for repeat encounters with the peptide antigen to which they have matured. This secondary exposure typically results in an anamnestic T cell response as these central memory cells expand and mature to an effector phenotype resulting

in an accelerated and more robust response to “recall” antigen. Thus, it is not surprising that central memory T cells are characteristically long-lived, turning over more slowly than effector memory cells [75] and in murine [76,77] and human [78] systems, they are relatively resistant to death signals after activation. We have found that the circulating S phase T cells in HIV infection are predominantly cells of a central memory phenotype that have been activated to enter cell cycle by bystander mechanisms [45] and that these S phase T cells infrequently complete cell cycle but instead tend to die *in vitro* [45,66]. This bystander cell death is reminiscent of the bystander cell death noted by several groups in lymphoid tissue in persons with chronic HIV-1 infection [79–81] although in those studies the phenotypes of the dying cells were not clearly defined. Recent studies suggest that in health, the long survival of central memory cells and resistance to death signals may be mediated through phosphorylation and inactivation of FOXO3a, resulting in retention of this transcription factor in the cytoplasm and diminished levels of the pro-apoptosis factor Bim. [82]. Not surprisingly then, the relative resistance of central memory cells to death signals is abrogated in HIV-1 infection [45,66] and recent work suggests that this might be related to activation of the FOXO3a pathway as in HIV-infected persons who manage to control HIV replication in the absence of therapy (“elite controllers”), the FOXO3a pathway tends to be inactivated in central and effector memory CD4+ T cells while it is activated in CM and EM cells of HIV-1-infected persons who have had viremia controlled with antiretroviral therapy and among healthy controls [83]. It should be noted however, that in HIV-1 infection both CD4+ and CD8+ T CM T cells are activated to enter cell cycle *in vivo* and yet, in contrast to CD4+ T cells, numbers of CD8+ T cells are not diminished until late in HIV-1 infection and are typically increased especially in early disease [84,85]. It is not clear whether the same or different factors are responsible for driving CD4+ CM T cells and CD8+ CM T cells into cell cycle. Irrespective, the relative survival and expansion of CD8+ T cells may be related at least in part to the greater capability of CD8+ T cells to expand after lymphocyte depletion [86]. Other factors also may contribute to the relative loss of CD4+ T cells and preservation of CD8+ T cells in HIV-1 infection. These include the susceptibility of activated CD4+ T cells to cell death as a direct consequence of cytopathic HIV infection. Also, the HIV-1 envelope protein can bind to cell surface CD4 and induce cellular activation and death [87]. In this regard, the relative shortening of telomeres among circulating CD8+ T cells but not CD4+ T cells in chronic HIV infection indicates that the surviving CD8+ T cells have undergone far more rounds of successful division than have the surviving CD4+ T cells [88]. Studies in the SIV-infected rhesus macaque also demonstrate profound activation and turnover of CM CD4+ T cells, which in that system migrate rapidly to tissue sites where they are thought to be at increased risk for SIV infection and death [89, 90]. We propose that immune activation in secondary lymphoid tissues is central to the pathogenesis of immune deficiency in chronic HIV-1 infection. In this model, effector T cells are inappropriately sequestered in lymphoid tissues; heightened inflammatory cytokine expression at these sites drives bystander entry of central memory CD4+ T cells into cell cycle and results in their accelerated turnover and death. Deposition of collagen as a result of sustained inflammation results in fibrosis, that interferes with cellular trafficking in the lymph node. As a result, anamnestic responses are impaired. At the same time, homeostatic signals to naïve T cells are also impaired resulting in a failure of naïve T cell expansion capacity and homeostasis. How does this happen?

In chronic HIV infection, secondary lymphoid organs are often enlarged and inflammatory

Generalized lymphadenopathy was one of the characteristic manifestations of the AIDS epidemic, even before its etiology was recognized [17,18]. This adenopathy is profoundly inflammatory [22,23] and is characterized by heightened expression of adhesion molecules [21] promoting dramatic lymphocyte sequestration and prolonged exposure to a localized

"cytokine storm". Bystander lymphocyte death in these tissues is characteristic [79–81], but the drivers of activation-related cell death at these sites are not known. With sustained inflammation at these sites, there is increasing deposition of collagen that results in fibrosis [91]. This fibrosis is thought to disrupt normal communication channels in lymphoid tissue and is associated both with a diminished number of circulating naïve T cells in HIV infection and also with failure of CD4 T-cell restoration with antiviral therapies [25,92]. With the availability of combination antiretroviral therapies, suppression of HIV replication was associated with increases best defined as biphasic in circulating CD4+ T cells [70,93,94] (as well as increases in other lymphocyte populations). The rapid first phase of cellular restoration after suppression of viral replication was associated with dramatic resolution of lymphadenopathy, and these findings were interpreted to reflect a redistribution of sequestered lymphocytes from the secondary lymph nodes to the circulation [21,94–96].

Why are the lymph nodes in HIV infection so inflammatory?

As noted above, HIV replication within lymphoid tissues provides high levels of viral antigen at these sites of immune homeostasis. Thus, there is reason to expect that effector T cells might be attracted and retained at these sites of high antigen density. And it does appear to be the case that the proportion of effector T cells in HIVinfected lymphoid tissue exceeds significantly their proportions in the nodes of healthy controls [29–32]. But is it is difficult to be confident that antigen density alone is sufficient to explain the hyperplastic lymph node response to HIV-1 infection. As examples, with similar clearance rates from plasma, daily production of virions in hepatitis C virus infection exceeds that of HIV by more than an order of magnitude [97] and in chronic hepatitis B infection, viremia typically exceeds that seen in HIV-1 infection by 2 to 3 orders of magnitude or more [28]. In HIV infection, though estimates are admittedly rough, the density of HIV antigen in lymphoid tissue is thought to exceed that in plasma by something more than 3 logs [98]. Thus, assuming that hepatitis virus antigens are neither concentrated nor excluded from lymphoid tissues, concentrations of HIV antigens at these sites during chronic HIV infection are likely to approximate those of hepatitis viruses in chronic liver infections. Therefore, it is reasonable to ask if factors other than antigen density contribute to the accumulation of effector cells and the inflammatory nature of the lymph nodes in HIV infection. Moreover, while there may be a relative accumulation of HIV-reactive cytotoxic T cells at these sites [29,31,32], their frequency is not sufficient to account for the total accumulation of effector cells in these inflammatory sites [30]. Conceivably, initial attraction and retention in lymphoid tissue of HIV-reactive effector cells during an acute early infection may establish inflammatory conditions and heightened adhesion molecule expression to trap and retain, by nonspecific mechanisms, effector T cells of diverse specificities.

Multiple microbial elements contribute to immunoactivation

But wait, there's more! Recent work in acute HIV infection [30,99,100] that are strikingly similar to findings in the SIV-infected rhesus macaque [101–103] indicate that within the first several weeks of HIV infection, the vast majority of effector/memory CD4+ T cells in the gut-associated lymphoid tissue (GALT) are dramatically depleted. This is a stunning finding as most mucosal immunologists contend that GALT contains the majority of the total T-lymphocyte population [104,105]. Though this is the prevailing and most supported view, this estimate has recently been questioned [106]. Nonetheless, not more than 2% of the total lymphocyte population can be found in circulation, thereby indicating that the modest depletion of circulating CD4+ T cells recognized in early HIV infection severely underestimates the magnitude of the actual memory/effector CD4+ T cell loss Surprisingly, this devastation has precious few clinical consequences, at least in the short terms the symptoms of acute HIV infection characteristically resolve and most HIV infected persons suffer few major clinical complications of immune deficiency until circulating CD4+ T cell counts fall to fewer than

200/uL and this characteristically takes years (longitudinal studies indicate that approximately half of HIV-infected persons remain AIDS-free for 10 years after acquisition of infection [107]). Why such profound depletion of the host effector memory CD4+ Tcell population is so well-tolerated for so long is not at all clear since it is at mucosal sites that microbial invasion often occurs. Nonetheless, throughout this period, progressive depletion of circulating CD4+ T cells is the rule but the pace of these losses varies enormously in the infected population [108,109]. As noted earlier, immune activation indices may predict the pace of CD4 depletion and onset of clinical immune deficiency better than does the magnitude of HIV replication (at least as reflected in plasma levels of HIV RNA [56,57]). How then does HIV infection result in immune activation? One model, as above, proposes that it is the influx and retention of HIV-reactive effector cells in secondary lymphoid tissues that may be driving immune activation via elaboration of pro-inflammatory cytokines. But there also may be long-term consequences of the extensive damage to the GALT lymphoid population that may contribute to this process as well.

The surface area of the human gut is enormous and does not comprise only the internal diameter of the lumen. Rather, the human gut surface area exceeds that of a tennis court [110]. This is necessary to promote absorption of nutrients and water. Yet at the same time, the gut's insides are really outsides for the human body and both small and large bowel are heavily colonized with bacteria with an estimated total bacterial population of up to 100 trillion [111]. In fact there are 10 times more bacterial cells in our gut than the total number of our own cells in the entire body. Somehow absorption of nutrients and water must take place without permitting microbes or microbial elements systemic access. In health, the gut mucosa (and perhaps otherbarriers) manage to limit systemic distribution of microbes and their products. In chronic HIV-1 infection, the gut mucosa seems surprisingly permeable to the systemic translocation of microbial products. In recently published work, Brenchley et al found high levels of bacterial lipopolysaccharide (LPS) in the plasma of persons with chronic HIV infection indicative of enhanced translocation of microbial products from the gut [112]. Levels of LPS were correlated with indices of T cell activation and with plasma levels of interferon-alpha and inversely predicted the magnitude of CD4 T-cell restoration after application of HAART. Moreover, in the pathogenic (rhesus) model of SIV infection, LPS levels were increased in infected animals, while in the non-pathogenic (sooty mangabey) model, SIV infection did not increase plasma LPS levels [112]. It is not just LPS that manages to translocate systemically in HIV infection. We have recently found high levels of bacterial DNA sequences in the plasma of persons with chronic HIV infection (Jiang ms submitted). Though bacterial DNA levels fell with application of HAART, they correlated poorly with plasma levels of HIV RNA. Not surprisingly, bacterial DNA levels correlated with levels of LPS and also correlated with indices of immune activation and predicted the magnitude of cellular restoration after application of HAART. The demonstration of elevated circulating levels of LPS and bacterial DNAs in plasmas of HIV-1-infected patients suggests that other microbial elements such as for examples flagellins, peptidoglycans, and other cell wall elements may also translocate into the systemic circulation in HIV infection but this has not yet been demonstrated.

Bacterial LPS and certain bacterial DNA sequences (most typically unmethylated CpG sequences) are representative of a number of microbial motifs that can activate innate immune responses via binding and signaling through host toll like receptors (TLRs). These motifs can be found in bacteria, fungi and also viruses and provide, via TLR binding, early recognition of microbial invasion [113]. Importantly, uridine-rich RNA sequences derived from the HIV genome are also capable of signaling through TLRs 7 and 8 [114–116]. Recently, we have found that each of 8 different toll like receptor agonists (including LPS (TLR4 agonist), CpG DNAs (TLR9 agonist), and agonists of TLRS 1/2, 3, 5, 7, and 8) could drive bystander T-cell activation and death. Naïve T cells were minimally affected by TLR ligand exposure while effector and memory phenotype cells were activated profoundly [117]. Interestingly, CM and

EM CD8+ T cells were activated to express the C-type lectin CD69 that in animals (and possibly in humans) promotes sequestration of activated T cells in lymphoid tissues via blocking surface expression of the sphongosine-1 phosphate receptor ($S1P_1$) [118]. Importantly, this pathway is type-1 interferon inducible [118]. In contrast to findings with CD8+ T cells, CM and EM CD4+ T cells were activated after exposure to TLR agonists to enter the cell cycle. Exposure to TLR ligands promoted cell cycle entry and death of both CD4+ and CD8+ CM and EM T cells but importantly the death signals were dramatically greater in CD4+ T cells than in CD8 + T cells [117]. How these microbial elements permeate through the damaged gut mucosa in HIV infection remains to be determined but very recent work indicates that helper CD4+ T cells of the Th17 phenotype in the gut are selectively depleted in pathogenic HIV-1 and SIV infections but much less so in nonpathogenic SIV infection and in HIV-1infected persons who do not experience progressive immune deficiency[119–122]. Th17 CD4 T cells are thought to play important roles in the control and clearance of extracellular pathogens such as bacteria and fungi [4] and may also play a role in induction of endogenous host defense peptides from epithelial cells [123]. It is therefore plausible to propose that their depletion in the GALT predisposes to systemic translocation of a variety of bacterial products.

So there is reason to propose that HIV, via interactions with TLR 7,8 and microbial elements that translocate from the gut and interact with other TLRs, can drive immune activation that results in activation and turnover of central memory and memory/effector CD4+ T cells and an entirely different activation phenotype of effector CD8+ T cells. Other infecting microbes also may contribute to immune activation in chronic HIV-1 infection. Recently, we found that in human lymphoid tissue explants, HIV-1 infection activates bystander cells creating new target cells not only for itself, but also for other viruses such as cytomegalovirus (CMV) [124,125]. Conceivably, CMV and other herpesviruses capable of infecting lymphoid tissue also may contribute to bystander immune activation via TLR ligation or by other mechanisms that may drive HIV-1 pathogenesis.

So in this model, replication within lymphoid tissues of HIV (and perhaps other lymphotropic copathogens) promotes heightened accumulation of effector T cells in secondary lymphoid tissue. At the same time, the accumulation of translocated bacterial (as well as locally expressed) TLR ligands enhances the immune activation and cytokine storm in lymphoid tissues. This heightened inflammation drives both the activation and turnover of central memory CD4+ T cells of diverse specificities accelerating their loss. These activated central memory cells also become increasingly susceptible to productive HIV infection [90]. At the same time, effector/memory CD8+ T cells are activated and inappropriately sequestrated in lymphoid tissue as a result of TLR ligand-induced CD69 expression and intracellular retention of S1P1. This further amplifies this inflammatory environment. At these sites, central memory CD4+ T cells are especially activation to enter cell cycle and die resulting in their progressive depletion. As these nodes become progressively fibrotic, the key cellular interactions necessary to promote appropriate Tcell homeostasisespecially those that promote naïve Tcell survival and expansion capacityare progressively lost, resulting in a failure of homeostatic proliferation as well as a failure of expected expansion and maturation in response to neoantigen stimulation.

Summary

It is perhaps embarrassing and surprising that after more than 25 years of study, immunologists and virologists have not yet figured out how HIV infection results in progressive CD4+ Tcell depletion. Our efforts to explain these losses can be likened to the old Hindu parable of 6 blind men asked to describe an elephant. Each reaches for a different part of this complex animal and each describes the elephant as a whole that reflects the part he has touched first and knows best. Like these blind men, we have all characterized the immune deficiency of HIV infection using the models and systems that are nearest to our own parochial interests and understanding.

The authors would like to take this opportunity to apologize to the other blind men who have developed different perspectives on the pathogenesis of immune deficiency in HIV-1 infection. Our failure to explore and discuss their models in detail does not indicate our lack of respect for their work. Rather we have taken this opportunity to promote our own ideas and we encourage our colleagues to do the same. On the one hand, one might even argue that the complexity of HIV pathogenesis is a defense that HIV has "used" to obscure our understanding and to block our efforts to contain it. Perhaps recognition of the complexity of HIV pathogenesis will be a good start to efforts to fully understand how HIV infection drives immune deficiency. With this in mind, we should be able to explore novel methods to interfere with downstream determinants of disease pathogenesis. Blocking immune activation may be one of them. Interventional studies will concurrently test and perhaps confirm models of pathogenesis that are only inferred from the data sets above and also may identify novel approaches to treatment of this pandemic infection.

Acknowledgments

The authors would like to acknowledge the Center for AIDS Research at Case Western Reserve University for logistic and financial support and the BBC/CLIC (Bad Boys of Cleveland/Cleveland Immunopathogenesisi Consortium) for helpful discussions and presentations that helped to frame the outline of this pathogenesis model.

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