Seminars in Immunology 20 (2008) 196–203

Contents lists available at ScienceDirect

Seminars in Immunology

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

Review

Lymph node architecture collapse and consequent modulation of FOXO3a pathway on memory T- and B-cells during HIV infection

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ARTICLE INFO

Keywords:
Lymph nodes architecture
Memory T cell
Memory B cell
FOXO3a pathways
HIV infection

ABSTRACT

Lymph nodes (LNs) represent the principal site where antigen-specific memory T- and B-cell responses are primed and differentiated into memory and effector cells. During chronic viral infections such as HIV, these lymphoid tissues undergo substantial structural changes. These changes are mostly caused by an imbalanced cytokine milieu, hyper-immune activation and collagen deposition leading to fibrotic LNs. The structural integrity of the LNs is essential to prime and maintain memory responses. Because cellular signalling events both up- and down-stream of FOXO3a are critical to the generation and the maintenance of lymphocyte memory, this review will focus on the interplay between the deregulation of the immune system caused by the virus and its impact on FOXO3a.

1. LNs, organized structures where immune cells initiate pathogen-specific responses

Lymph nodes (LNs) are small bean shaped structures spread along the lymphatic vessels where cellular interactions between lymphocytes and antigen-presenting cells (APCs) lead to the initiation of humoral and cellular immune responses. LNs display three architectural parenchyma components: the germinal centers (GCs), the cortex and the paracortex.

The paracortex is the predominant site of initiation of the immune response. It harbors several T-cell subsets and APCs, both responsive for the generation of effector and memory T-cells. Indeed, the functional architecture of LNs can be described as an interface between a network of APCs and a population of highly migratory lymphocytes [1]. Therefore, in the context of HIV infection, resting T-lymphocytes circulate in the bloodstream, enter the LN through lymphatic afferent vessels and migrate through the network of APCs (guided by chemokine gradients) and interact with antigens. These interactions lead to the activation of T-cells which undergo clonal proliferation and to the development of memory T-cells.

On the other hand, the generation and preferential survival of antigen-specific memory B-cells with enhanced affinity, a phenomenon known as affinity maturation, are critically dependent on the formation of GCs. Indeed, GCs contain APCs such as macrophages and follicular dendritic cells (or FDCs) representing the antigen capture zone for B-cell maturation [2,3]. Therefore, GCs provide an optimal environment for B-cell proliferation, immunoglobulin variable region gene diversification by somatic hypermutation, and the selective survival of clones with enhanced affinity [4,5]. Upon interactions with antigen-pulsed APCs, GC B-cells differentiate into memory B-cells or antibody secreting plasma cells, which then re-circulate in the periphery [6,7]. Of note, activated T-cells play a critical role in the generation of memory B-cells via soluble cytokines (i.e., IL-4) and cell–cell interactions (i.e., CD40–CD40L).

The maintenance of the LN structural and functional integrity ensures the generation of efficient immune responses by providing the ground for the appropriate priming of T- and B-cells [8–13]. The disruption of the LN architecture during HIV infection, as will

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1044-5323/$ – see front matter © 2008 Published by Elsevier Ltd.
doi:10.1016/j.smim.2008.07.008

be described below, leads eventually to a profound perturbation of T- and B-cell homeostasis impacting negatively on the generation and maintenance of memory populations.

2. Events observed in LNs during HIV infection

2.1. Early viral dissemination into LNs during HIV infection

One of the earliest events occurring after mucosal HIV transmission is viral "seeding" into draining LNs, where large quantities of viruses are trapped in follicular GCs [4,14,15]. DCs present at the initial sites of virus entry are key players in scavenging and transporting HIV particles and processed antigens from the periphery to the LNs [16,17]. Indeed, HIV replicates heavily in the gut-associated lymphatic tissues (GALT) following entry into the mucosal tissues; GALT in mammals includes more than 40% of total body lymphocytes [18,19]. The high levels of *de novo* recruitment of naïve T-cells into the lymphoid tissues further provide breeding grounds for HIV replication and global viral dissemination.

In HIV-infected individuals, a large number of latently infected $CD4^+$ T-lymphocytes and macrophages are also detected throughout the lymphoid system from earliest to the more advanced stages of infection [20]. A more precise estimation of the contribution of LNs to the viral burden has been possible through the development of sensitive RNA quantification methods. During the transition from primary to chronic HIV infection, the level of HIV replication in lymphoid tissues remains elevated despite the fact that viremia is significantly down-regulated in periphery [21]. These studies demonstrate that a heavy viral load does indeed reside in LNs, confirming that the latter may function as a major anatomical "reservoir" for HIV [22]. Both the strength and persistence of viral replication within LNs can explain the chronic stimulation of resident T-cell populations and the progressive breakdown observed in the lymphoid architecture [14,23].

2.2. Alterations observed in LN architecture during HIV infection

The non-human primate model has provided ample information to better examine the impact of HIV infection on the integrity of LNs architecture. Using the non-human primate model, Estes et al. have determined the kinetics and the onset of the disruption of LN architecture. They have reported the deposition of collagen type I, a major hallmark of LN architecture disruption, in the lymphatic vessels as early as day 7 following infection with SIV. The onset of collagen deposition coincided with heightened immune activation state and increased frequencies of transforming growth factor beta 1 (TGF-β1)-positive regulatory T-cells. Collagen type 1 deposition in the lymphatic tissues of SIV-infected rhesus macaques by day 7 following infection could be due to TGF-β1 over-expression and may irreversibly disturb lymphoid homeostasis as T-cells are not receiving the appropriate survival signals from APCs in the LN [24]. Similar observations have been made in the context of HIV infection, where collagen deposition is observed in the T-cell zone within the LN paracortex [25]. This TGF-β1-mediated fibrosis is capable of disrupting cell–cell interactions and will prevent the exposure of lymphocytes to the cytokines and cellular signals that are crucial to the maintenance of a balanced T-cell pool [26].

APCs are altered during HIV infection and the loss of these cells will inevitably impact on T-cell survival and on the maintenance of memory lymphocyte subsets [16,27,28]. Accordingly, tissues isolated from HIV-infected individuals display a dramatic depletion of both myeloid (mDCs) and plasmacytoid (pDCs) DCs [29]. In more advanced disease stages, organized GCs also disappear as evidenced by a decline in the extent of the FDC network [14,30]. Mueller et al. have clearly observed a progressive breakdown of the LN architecture, especially of the FDC network in LN biopsies from several HIV-infected children [31]. Similar observations have been made *in vivo* in murine-acquired immunodeficiency syndrome and in SIVsm (strain SMM-3)-infected cynomolgus monkeys [23,27,32].

Persistence of viral replication in the LNs is associated with the establishment of a chronic immune activation state, partially characterized by the infiltration of cytotoxic $CD8^+$ T-cells. Massive infiltrations of cytotoxic $CD8^+$granzyme-B^+ T-cells are very obvious in the LNs and are observed early in the first weeks after HIV infection [4]. The expression of several cytokines (such as IL-1β) is also chronically up-regulated within LNs. The high expression levels of inflammatory cytokines present in LN environment lead to (1) significant increases of the expression of CD38 and CD95 (or Fas receptor) in resident T-cell populations, (2) heightened sensitivity to Fas-mediated apoptosis and (3) progressive loss of the total $CD4^+$ T-cell population [4,29,33,34].

2.3. Will the decrease of viral load by anti-retroviral therapies restore the integrity of LNs architecture?

Despite the overwhelming success in limiting HIV viral load and reducing many of HIV pathogenic effects, highly active antiretroviral therapy (HAART) partially restores LN architecture in HIV-infected patients [14,33]. In fact, some LN alterations are still present under HAART treatment, most probably caused by the residual viral load [28,35–37]. Viral persistence occurring during HAART is explained by the early establishment after infection of a significant pool of latently infected cells. This HIV "reservoir" persists for many years within LNs and participates to the maintained viral replication by homeostatic proliferation and/or by T-cell activation (N. Chomont, unpublished data) [21,22,38]. The persistence of local inflammation induced by the hyper-immune activation and viral replication negatively impacts on the priming of naïve T-cells and thus limits the overall recovery of the immune response [25]. It also impedes on memory T-cell survival even in successfully treated aviremic individuals [39].

2.4. Do long-term non-progressors (LTNPs) display intact LN architecture and effective immune function?

LTNPs represent a rare group of HIV infected (1/300) and untreated patients who display control of the HIV replication and show no signs of disease progression. LTNPs maintain weak plasma viremia and high peripheral $CD4^+$ T-cells counts (>400 cells per mm^3) for years [40–42]. The preservation of LN architecture and the lack of heightened state of immune activation observed in these subjects could explain why LTNPs demonstrate persistent and potent T- and B-cell responses [39,43,44].

2.5. Is non-pathogenic SIV-infection in non-human primates associated with the maintenance of LN architecture?

Similarly to LTNPs, a number of species of "old world monkeys" (i.e., African green monkeys, Sooty mangabeys) do not develop AIDS-related illnesses despite the persistence of high viremia [45–47]. Interestingly, these monkeys, unlike SIV infection in rhesus macaque, do not develop high levels of immune activation; frequencies of TGF-β1 producing T_{reg} cells do not increase in these monkeys which could explain the lack of collagen deposition associated LNs architectural destruction [24]. Moreover, sooty mangabeys do not display any evidence of follicular fragmentation, which can be considered to be an advanced stage of lymphoid disruption [48,49]. This suggests that the infiltration of activated cytotoxic $CD8^+$ T-cell populations and chronic immune