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Role of resident CNS cell populations in HTLV-1-associated neuroinflammatory disease

Veronique Lepoutre, Pooja Jain, Kevin Quann, Brian Wigdahl, Zafar K. Khan

Department of Microbiology and Immunology, and Center for Molecular Virology and Neuroimmunology, Center for Cancer Biology, Institute for Molecular Medicine and Infectious Disease, Drexel University College of Medicine, Philadelphia, Pennsylvania 19102, USA

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1. ABSTRACT

Human T cell leukemia virus type 1 (HTLV-1), the first human retrovirus discovered, is the etiologic agent for a number of disorders; the two most common pathologies include adult T cell leukemia (ATL) and a progressive demyelinating neuroinflammatory disease, HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP). The neurologic dysfunction associated with HAM/TSP is a result of viral intrusion into the central nervous system (CNS) and the generation of a hyperstimulated host response within the peripheral and central nervous system that includes expanded populations of $CD4^+$ and $CD8^+$ T cells and proinflammatory cytokines/chemokines in the cerebrospinal fluid (CSF). This robust, yet detrimental immune response likely contributes to the death of myelin producing oligodendrocytes and degeneration of neuronal axons. The mechanisms of neurological degeneration in HAM/TSP have yet to be fully delineated *in vivo* and may involve the immunogenic properties of the HTLV-1 transactivator protein Tax. This comprehensive review characterizes the available knowledge to date concerning the effects of HTLV-1 on CNS resident cell populations with emphasis on both viral and host factors contributing to the genesis of HAM/TSP.

2. INTRODUCTION

Human T cell leukemia virus type 1 (HTLV-1) is a type C retrovirus primarily endemic to Japan, Central and South America, the Middle East, regions of Africa, and the Caribbean (1-7). Currently, an estimated 10-20 million people worldwide are infected with this virus (8-10). Although the majority of infected individuals remain asymptomatic, HTLV-1 is the causative agent of a number of disorders, notably adult T cell leukemia (ATL) and a progressive demyelinating neurologic disorder, HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) (11). HTLV-1 presents as either ATL or HAM/TSP in approximately 2-3% of seropositive individuals after a long asymptomatic period of latency (12). The likelihood of a small percentage of HTLV-1-infected patients developing HAM/TSP has been postulated to be dependent on several factors including human histocompatibility leukocyte antigen (HLA) subtype (13), viral strain (14-16), mode of infection (17), and proviral DNA load (18-22). In addition to ATL and HAM/TSP, HTLV-1 has been associated with a spectrum of extraneural inflammatory disorders such as pulmonary alveolitis, dermatitis, Sjogren's syndrome, Becet's Disease, thyroid disease, prostatitis, cystitis (23), uveitis, arthritis, hepatitis (24), polymyositis, HTLV-1-associated

arthropathy, and a syndrome clinically indistinguishable from sarcoidosis (25).

3. HTLV-1-ASSOCIATED MYELOPATHY/TROPICAL SPASTIC PARAPARESIS (HAM/TSP)

The predominant neurological disorder caused by HTLV-1, HAM/TSP, is a chronic progressive inflammatory disease with many similarities to multiple sclerosis. Pathologically, HAM/TSP is manifested as a demyelinating disorder involving degradation of white matter within the lateral funiculi spinal cord, mainly concentrated in the thoracic and lumbar segments of tissue. Degeneration has also been described in the cervical spinal cord and the brainstem, although this may be due to secondary damage from Wallerian degeneration (26, 27). The main area of neuronal damage has been observed within the corticospinal tract, with the majority of patients citing weakness of lower limbs as the first symptom (28). Clinically, HAM/TSP presents as a spastic paraparesis with common symptoms including lower back pain as well as urinary and sexual dysfunction (11, 29, 30). HAM/TSP is three times more likely to affect women than men (11, 29) and the disease progresses at a faster rate in women than in men. Progression is further increased if disease onset occurs before menopause, suggesting that hormones may be involved (31). HAM/TSP often occurs in two phases, initiated first as an inflammatory disorder, followed by a chronic long-term degenerative stage (32). Although there are a multitude of factors that are involved in the development and progression of HAM/TSP, symptomatic patients typically demonstrate the presence of HTLV-1-specific antibodies and infiltrating T lymphocytes in the peripheral blood and cerebrospinal fluid (CSF) accompanied by the release of proinflammatory cytokines (33, 34). This inflammatory response compromises the integrity of the blood-brain barrier (BBB) and increases the potential for further lymphocyte trafficking into the CNS (35-38). $CD8^+$ cytotoxic T lymphocyte (CTL) cells specific for the HTLV-1 transactivator protein Tax, especially the Tax11-19 amino acid epitope, have been shown to be the primary proliferating cell type in HAM/TSP (39). Later stages of the disease are marked by the presence of extracellular Tax and expanding Tax-specific CTLs in the CSF (40-43).

There are several contributing mechanisms postulated to be involved in the demyelination and CNS cell death that occurs in the spinal cord of HAM/TSP patients: the direct damage mechanism, the bystander mechanism, and the autoimmune mechanism of molecular mimicry (44). The direct damage mechanism involves damage caused by infiltrating activated $CD8^+$ CTL cells specific for Tax. The persistent activation of $CD8^+$ T cells in the CNS suggests the continued presence of replicating virus or viral proteins (45). Cellular damage in the direct damage model results from the targeted lysis of infected cells and release of inflammatory molecules. The bystander damage mechanism involves the damage in the CNS that is caused by cytotoxin release, specifically proinflammatory cytokine release, by the infiltrating lymphocytes and resident cell populations in response to the presence of HTLV-1 (46). Proinflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interferon-γ (IFN-γ) are postulated to cause dysfunction and death to resident cells of the CNS with further disruption of the BBB (47). In addition, HTLV-1-associated pathogenesis within the CNS may be associated with an autoimmune mechanism involving molecular mimicry. An immune response generated to the viral protein Tax was found to cross-react with the neuronal antigen heterogeneous ribonuclear protein-A1 (hnRNP-A1) (44, 48). Thus, a CTL response directed against Tax could lead to the incidental lysis of hnRNP-A1-presenting cells in the CNS.

4. CNS RESIDENT CELL POPULATIONS AND HAM/TSP

A number of the resident CNS cell populations during the course of HAM/TSP have been shown to be susceptible to viral infection. Based on numerous *in vitro* studies, animal model investigations, and studies performed in human tissues, the existence of latent, persistent, and productive viral infection of resident cell populations is likely but the extent and the role of these infected cell populations with respect to the etiology of HAM/TSP remains under investigation (17, 49). In general, the main targets for viral infection are thought to be the cell populations responsible for regulating the BBB such as astrocytes, microglia, and peripheral immune cells. Oligodendrocytes and neurons, which form the core of the CNS, are also potential targets for HTLV-1. Experiments performed *in vitro* have successfully infected astrocytes, macrophages, microglia, and neurons with HTLV-1 (50), yet *in situ* PCR hybridization has localized proviral DNA in the CNS only to astrocyte cell populations and infiltrating $CD4^+$ T lymphocytes (20, 51), which have been postulated to be nonproductively infected. However, there exists the possibility that proviral DNA is present in other cell types but at levels below the limits of detection (17). The susceptibility of the resident CNS cell types to HTLV-1 infection and subsequent viral gene expression likely leads to cellular dysfunction coupled with clinically apparent neurologic dysfunction. In addition, viral-induced alterations in these cells may play important roles in the progression of HAM/TSP. However, very little information exists concerning the molecular mechanisms of HTLV-1 LTR activation and/or viral gene expression in the secondary target cell populations. Several members of the C/EBP family are expressed at high levels in cells of the monocyte-macrophage lineage (52) and are intimately involved in the regulation of myelocytic-monocytic gene expression. Recently it was shown that basal activation of HTLV-1 LTR was enhanced by the overexpression of C/EBPβ, C/EBPδ, or C/EBPε, whereas Tax-mediated transactivation was inhibited by the overexpression of C/EBPα and C/EBPβ, and to a lesser extent by C/EBPδ (53). This has indicated that cells expressing high levels of C/EBP factors such as some of those within the myeloid lineage are less permissive to HTLV-1 gene expression. In addition, the AP-1 family of transcription factors was also shown to modulate HTLV-1 LTR activation during phorbol ester-induced differentiation of monocytes from the $CD34^+$ progenitor cells (54). The binding sites for another family

of transcription factors (Sp1-Sp4) have also been identified within the U3 region of the HTLV-1 LTR (55). Both Sp1 and Sp3 were found to inhibit basal and Tax-mediated LTR activation by binding to Tax responsive element 1 (TRE-1) repeat III (55). Therefore, trafficking of latently and/or persistently infected monocytes can lead to viral transmission to the CNS and infection of resident cell populations.

4.1. Perivascular cells, macrophages, and microglia

Perivascular cells are derived from bone marrow monocytes and possess the ability to differentiate into a number of cellular phenotypes. These cells are located in the vascular area surrounding vessels supplying oxygenated blood to the CNS, which forms a bridge or link between the immune system within the peripheral blood and associated lymphoid tissues and the immune surveillance system within the CNS. Perivascular macrophages express major histocompatibility complex (MHC) class II antigens and are known to possess phagocytic properties and the ability to act as antigen presenting cells (APCs) (56, 57). These cells display a high turnover rate and may proliferate in circumstances associated with CNS inflammation. During the course of HAM/TSP, a small percentage of peripheral blood monocytes are infected, which enter the CNS as macrophages and perivascular microglia as they are replenished (58, 59). There are two populations of resident microglia in the CNS that include the perivascular and parenchymal microglia. Perivascular microglia reside near the CNS blood vessels and have a high turnover rate whereas parenchymal microglia have a lower turnover rate, surviving for nearly the life of the individual (59). Microglial cells function as the primary immune cell population within the CNS. These are macrophage-like cells of monocyte origin able to function as both APCs and phagocytes (60). The parenchymal microglial cells are normally a quiescent, small cell population within the CNS, able to replicate under inflammatory circumstances and acquire a reactive phenotype, a process also known as microgliosis (61). Unlike perivascular microglial cells, parenchyma microglia do not express major histocompatibility complex (MHC) class I or II in their quiescent state (57, 62-64). Positive correlations have been demonstrated between the HTLV-1 proviral DNA load and macrophage and microglia cellular activation (65). Hoffman *et al* successfully infected a monocyte cell line, microglia, and blood-derived macrophages with HTLV-1 *in vitro* in several mixed culture conditions. Their results suggested the ability of microglia and macrophages to harbor proviral DNA during chronic infection, but *in situ* hybridization has not corroborated these results *in vivo* as of yet (51, 66-69). Microglia have also been successfully transduced with Tax *in vitro*, subsequently releasing inflammatory cytokines including TNF-α, interleukin (IL)-6 and IL-1β, potentially contributing to the demyelination in the pathogenesis of HAM/TSP (70).

4.2. Astrocytes

Astrocytes are the most abundant CNS resident cells and are involved in the maintenance of the physical integrity of the BBB. Astrocytes mediate the physiological environment of the CNS through their contribution to the BBB, as well as provide nutrient factors to neuronal cells, maintain the structural integrity of the CNS, and prevent incidence of cell death through excitotoxicity by the uptake of the excitatory transmitter glutamate (71-73). Astrocytes are also thought to have the capacity to function as immune cells together with microglia, and are controversially suggested to act as non-professional APCs (64). Activation of these cells induces the secretion of proinflammatory cytokines and chemokines, and subsequently the recruitment of antigen-specific $CD4^+$ and $CD8^+$ T-cells from the periphery (74). Due to the sheer number of astrocytes, the variety of functions performed, and their importance to the CNS environment, they have been examined with respect to their potential role in the genesis of HAM/TSP. The proximity of the astrocytes to the BBB places these cells in a vulnerable position to be infected through cellular contact with infiltrating HTLV-1-infected lymphocytes and/or monocyte-macrophages. *In situ* hybridization studies have localized HTLV-1 Tax RNA in the CNS to astrocytes, suggesting that astrocytes may also be a source of extracellular Tax in the CNS through secretion (51). In support of these observations, we have also demonstrated the secretion of the HTLV-1 Tax protein from astrocytes cultured *in vitro* (unpublished observations). Banerjee *et al* performed an *in vitro* Tax transduction of an astrocytoma cell line that resulted in both the release of proinflammatory cytokines as determined by a proinflammatory cytokine array. These studies also demonstrated that serum-starved primary astrocytes were sensitive to apoptosis when treated with Tax (75). Tax- and TNF-α-treated reactive astrocytes have also been shown to downregulate their uptake of glutamate and catabolism to glutamine by the decreased mRNA expression of glutamate transporters, thereby potentially contributing to the increased incidence of neuronal and oligodendrocyte death or dysfunction by excitotoxicity (76). Relevant to these *in vitro* studies, additional *in vitro* experiments have suggested that HTLV-1 infection of astrocytic cultures results in the initial production of infectious virus with the subsequent establishment of a latent infection (77-81). This infection may be temporarily reactivated by the administration of proinflammatory cytokines (78, 82). Overall, the available evidence has suggested that astrocytes may act as a viral reservoir within the CNS (83).

4.3. Neurons

Although neurons are not believed to harbor virus *in vivo* (51), the potential for HTLV-1 neuronal infection *in vitro* was demonstrated by the infection of a neuroblastoma cell line, and a neuronal cell line of non-tumorgenic origin, HFGC and HCN-1a (84). The presence HTLV-1 surface antigens was verified by *in situ* hybridization and flow cytometry (85). As discussed previously, another reported mechanism of neuronal damage in HAM/TSP may be due to the autoimmune pathology of molecular mimicry, which as been shown to involve the recognition by the immune system of a host antigen as a viral protein. Host targets have been demonstrated to be the hnRNP-A1 neuronal self-antigen, a nuclear riboprotein, and the similar but shorter $hnRNP\text{-}A1^B$. These proteins have been identified as cross-reacting

Table 1. Host and viral factors in HAM/TSP neurological pathology

Cell type	HAM/TSP		
	Clinical Pathology	Susceptibility to Infection	Cytokine/Chemokine
Macrophages/Microglia	Reactive gliosis (65)	In vitro (62)	TNF-α, IL-6, IL-1β (66)
Astrocytes	Reactive gliosis (65)	Restricted infection (51)	TNF-α, TNF-β, IL-1α, IL-β, IL-6, MMPs (71, 72, 90)
Neurons	Axonal dystrophy (65)	In vitro (80, 81)	TNF-α (84)
Oligodendrocytes	Demyelination (65)	Not demonstrated	IL-1β, TNF-α, TNF-β, IL-6 (71)

with anti-Tax antibodies, suggesting that Tax and neuronal proteins share some sequence homology. The molecular mimicry may lead to a CTL response directed against neuronal populations (27, 86). The cross-reactivity and presence of autoantigens may contribute to the pathogenesis of HAM/TSP, but is unlikely the primary cause, as hnRNP-A1 is not confined to the CNS nor easily detected (87). To examine the effect of extracellular Tax on neurons, the neuronal cell line NT2-N was treated with soluble Tax. The treatment of these cells with Tax, even for time periods as short as 5 min, resulted in gene expression and secretion of TNF-α. These results have suggested that neurons subjected to Tax *in vivo* may contribute to the immune pathogenesis of HAM/TSP (88).

4.4. Oligodendrocytes

As stated previously, the pathogenesis of HAM/TSP has been shown to involve a progressive demyelination resulting from the dysfunction and death of the CNS myelinating cell, the oligodendrocyte. Myelin is a fatty protein, composed of layers of plasma membrane that insulate axons and increase the speed of conduction and accuracy of neuronal electrical action potential impulses (89). In diseases such as multiple sclerosis (MS), it is generally thought that axonal degeneration will follow demyelination (90). There are two theories concerning the demyelination that occurs in HAM/TSP. The first, or "outside-in" theory, assumes that the oligodendrocyte damage occurs primary to the axonal degeneration (91). Moore *et al.* hypothesized that infiltrating $CD8^+$ T cells are responsible for the dysfunction and death of oligodendrocytes by the release of proinflammatory cytokines, and by the lysis of infected cells (26). Oligodendrocytes are inherently sensitive cells to the effects of TNF-α, one of the proinflammatory cytokines released by infiltrating $CD8^+$ T cells (43, 47, 92, 93). Extracellular Tax is able to induce proinflammatory cytokine secretion from the resident CNS cell populations as well, contributing to the dysfunction of oligodendrocytes. The "inside-out" theory, however, suggests that the axonal dysfunction occurs prior to the oligodendrocyte dysfunction. In this theory, the axonal degeneration is the primary pathology and oligodendrocyte death is a subsequent occurrence (91). Banerjee *et al.* demonstrated that an oligodendroglioma cell line will secrete the proinflammatory cytokines IL-1β, TNF-α, TNF-β, and IL-6 when transduced by Tax, as determined by cytokine array experimentation. Regardless of whether damage is caused by an "outside-in" or "inside-out" mechanism, the oligodendrocyte plays an integral role in the genesis of HAM/TSP (75). A summary of the CNS resident cells with respect to the genesis of HAM/TSP is shown in Table 1.

5. VIRAL FACTORS

Previous studies have suggested that the mode by which primary infection occurs is a potential factor that may determine whether an infected carrier progresses to develop ATL or HAM/TSP. An infection occurring through the peripheral blood, such as would occur through intravenous drug use, leads to the shuttling of $CD4^+$ infected T-cells to the bone marrow where they may subsequently transfer infectivity to progenitor cells as well as lymphoid and myeloid precursor cells populations. These cells then elicit tax-specific immune responses and cross over into the BBB to cause HAM/TSP (17, 94). Primary infection via mucosal linings, as would occur through sexual contact, involves the infection of APCs first, where they shuttle to lymph nodes and subsequently transfer infectivity to T cell populations, a weak HTLV-1-specific response is created and the T cells are allowed to proliferate ultimately leading to ATL (17). In addition to the cellular dysfunction resulting from viral replication within specific cell populations, viral proteins, such as Tax as well as other retroviral proteins, when secreted into the extracellular environment may be capable of causing damage independent of the direct damage caused by viral replication and that due to the immune response to infection. This section will discuss many of the viral factors associated with HTLV-1, including viral transmission and infection, and actions of Tax that are necessary for viral infection such as the transcriptional and extracellular effects of Tax. Host-viral interactive factors proposed to contribute to the development of HAM/TSP, such as mode of infection, HLA alleles, and proviral load are also included.

5.1. Viral transmission

Similar to HIV-1, HTLV-1 has a tropism for $CD4^+$ T-cells, although $CD8^+$ T cells (21), monocytes, dendritic cells (DCs) (58, 95-98), and as discussed previously, resident CNS cell populations, are susceptible to infection as well. The infection may occur through a variety of mechanisms. Infection of HAM/TSP patients involves a latent infection of the bone marrow compartment that is extended to the periphery through the process of hematopoiesis, possibly contributing to the viral burden in the $CD4^+$ T cell, $CD8^+$ T cell, macrophage, and DC compartments in the peripheral circulation and tissues (99, 100). A general feature associated with HTLV-1 infection involves the spontaneous proliferation of peripheral blood mononuclear cells when cultured *in vitro*. In HAM/TSP patients, this proliferation involves, to a large extent, virus-infected $CD8^+$ T cells (39). The mechanism of proliferation appears to involve the impact of Tax on the cell cycle and the increased release of IL-2 (101). The expansion of proviral DNA by cellular proliferation rather than by viral replication involving the activity of reverse transcriptase probably accounts for the genetic stability in the proviral DNA load observed compared to other retroviral infections such as those involving HIV-1 (102). In contrast to the hyperstimulated T cell response invoked

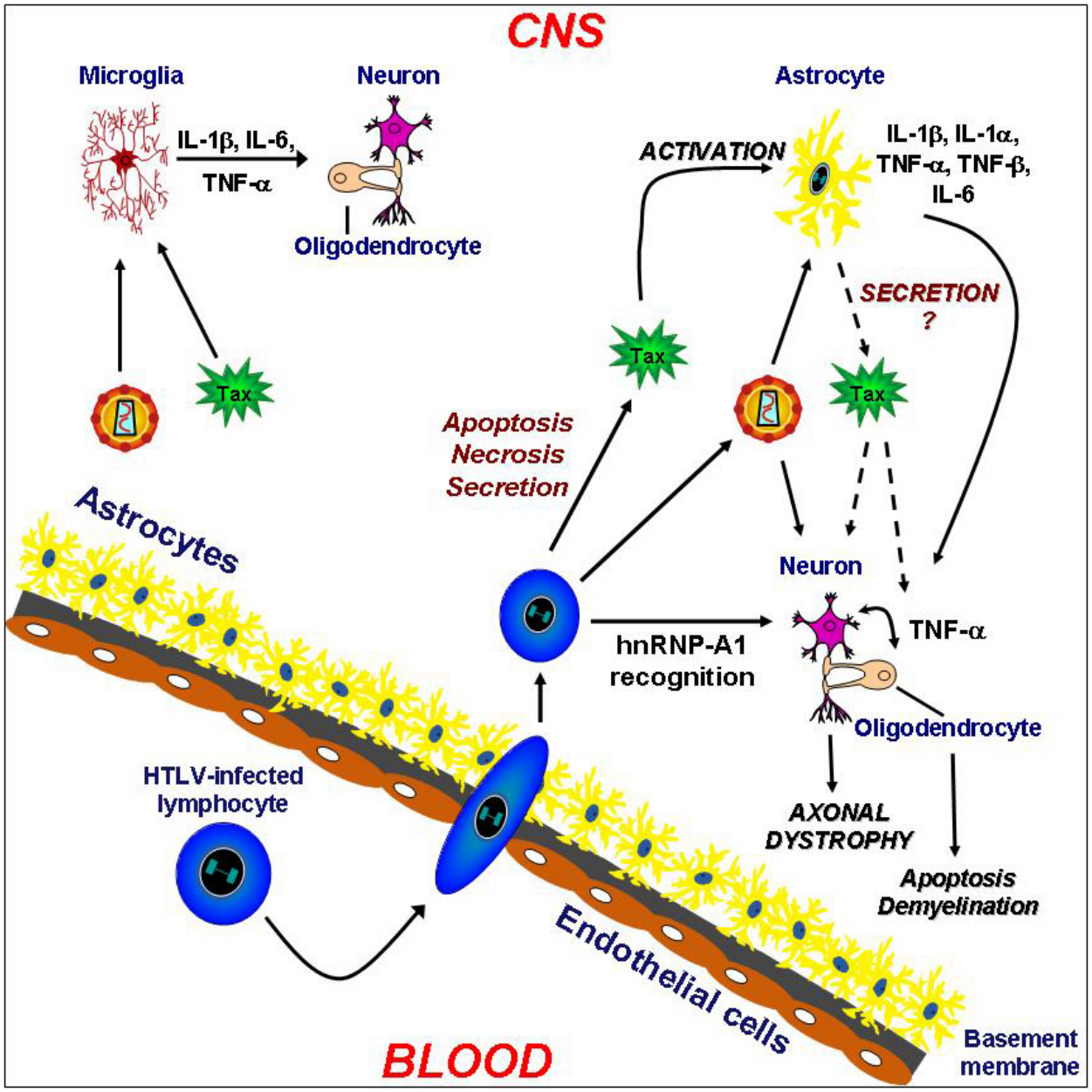

Figure 1. Resident CNS cells potentially involved in the genesis of HAM/TSP. The selectively permeable blood-brain barrier composed of endothelial cells, pericytes, and astrocytes is first penetrated by an HTLV-1-infected cell of lymphocytic or possibly monocytic origin. Spreading throughout the CNS, infection causes the release of the Tax protein as well as inflammatory cytokines that are responsible for demyelination and neuronal damage, causing symptomatic advancement of HAM/TSP.

by HTLV-1 infection, HIV-1 viral infection impairs the proliferation of $CD4^+$ T cells; there is in fact, a proliferation defect following receptor stimulation (103-106), followed by a decrease in IL-2 production and a progressive depletion of $CD4^+$ T cells resulting from greater susceptibility to apoptosis (103, 107-109). Direct HTLV-1 infection occurs via cell-to-cell contact rather than by cell-free virus, as only 1 in 10^5 free virions is infectious (110-112). It is generally thought that the low efficiency of the HTLV-1 virion infection involves a unique frameshifting that occurs in the synthesis of the reverse transcriptase. The Gag-Pol-Pro precursor has been shown to require two frameshift events during translation, contrary to one frameshift or the absence of frameshifting that appears to be common in other retroviruses. The downstream consequence relative to the formation of the three precursor protein/polyproteins (Gag, Gag-Pol, and Gag-Pol-Pro) may be a low ratio of enzyme activity to Gag protein. This may result in some viral particles containing no reverse transcriptase activity (113-115). The cell-cell transmission of HTLV-1 occurs through a structure termed the "virologic synapse". This process involves the

reorientation of the infected cell relative to the uninfected cell based on alterations induced in the microtubule-organizing center. This process has been shown to occur in response, at least in part, to the activity of the Tax protein, found to be located near the microtubule-organizing center. The polarization of the infected cell relative to the uninfected cell triggers the microtubule reorientation involved in forming the virologic synapse (112, 116). The Env protein (specifically, the surface gp46 protein) from an infected cell binds to the target receptor, often the ubiquitous glucose uptake molecule Glut-1. It is postulated that surface heparin sulfate proteoglycans, and neuropilin-1 may act as receptors as well (117-119). The intracellular adhesion molecule-1 (ICAM)-1, ICAM-3, and vascular adhesion molecule (VCAM) receptors may act as cofactors for the cellular fusion (120, 121). In the interaction between virus and DCs, the receptor DC-SIGN (dendritic cell-specific ICAM-3 grabbing non-integrin) acts as a cofactor for viral entry (122).

5.2. Proviral load

A strong indicator of disease progression from asymptomatic HTLV-1 infection to HAM/TSP is the presence of a high proviral load (18, 19, 22, 123). There is a large variation in the proviral load of HTLV-1-infected carriers, a 10- to a 100-fold increase may be observed in HAM/TSP patients compared to asymptomatic carriers (123, 124). Host genetic factors such as HLA class 1 genotypes are thought to be a factor relevant to both proviral load and CTL recognition, as the MHC class 1 alleles HLA-A*02 and HLA-Cw*08 are associated with lower proviral loads and have a protective effect on the acquisition of HAM/TSP while the HLA-B*5401 allele is associated with both a higher proviral load and risk of HAM/TSP. The alleles may be associated with CTL efficiency, as the CTL recognition of many viral epitopes contributes to anti-viral surveillance (125, 126). Although important for controlling proviral load, the CTL response is a contributor to resultant tissue damage through an overly active inflammatory response (45, 123, 125). An autoregulatory loop may develop between the proviral load and $CD8^+$ T-cells. As stated earlier, the proviral load appears to stimulate the amount of proliferating $CD8^+$ T cells, a large percentage of which will subsequently become infected, further increasing the proviral load (17). A CTL response is necessary to control HTLV-1, but in HAM/TSP, despite the large number of activated, circulating CTL cells, the proviral load remains elevated. It is possible that these cells are not effective, and are in fact deregulated by viral infection (44). This deregulation may be described through a three-cell model consisting of $CD4^+$ T-cells, $CD8^+$ T-cells, and DCs, which are able to activate a naïve $CD8^+$ T cell to become a CTL (127). Before this occurs, a DC needs to encounter an antigen, migrate to the lymph nodes, and present the antigen to $CD4^+$ T cells. Following recognition, the $CD4^+$ T cells are activated and express a costimulatory molecule such as CD40L that may then bind to the corresponding receptor on DCs and has been shown to induce their maturation. The mature DCs may then activate $CD8^+$ T-cells (44). HTLV-1 may infect all three of these cell types, and this may result in a deregulation of the resulting CTL activity (128-130). How infection may result in deregulation is not known for certain, but may be through the cellular interactions with $CD4^+$ T cells. Through the use of correlational studies, Wodarz and Bangham (131) calculated that in asymptomatic carriers a positive correlation exists between the CTL response and viral load, while in patients with HAM/TSP there was no correlation. These results strongly suggest that viral load and CTL activation may be responsible for the efficacy of the CTL response (131).

5.3. Transcriptional transactivator protein Tax

A key protein regulating the progression of HAM/TSP is the HTLV-1 transcriptional transactivator, Tax. The Tax protein, encoded from the pX region of the HTLV-1 genome, has been shown to activate both viral and cellular gene expression and has been thought to escalate the pathogenesis of HTLV-1 (132). Tax possesses the capacity to repress the cellular machinery responsible for DNA repair and may promote apoptosis, the expression of proto-oncogenes, and proliferation of T cells. These characteristics contribute to T cell transformation, and subsequently to the commencement of ATL (132-142). Tax is localized in both the nucleus and cytoplasm within cells. The nuclear accumulation of Tax is promoted by a nuclear localization signal (NLS) found within the first 58 amino acids of the amino-terminus of the protein, a signal that is unique when compared to classical NLSs (143, 144) in that the signal is suspected to involve some form of conformational element in addition to the cis-acting element. In addition. Tax contains a leucine-rich nuclear export signal (NES) and has been shown to be able to shuttle to and from the cytoplasm and nucleus (143, 145). Tax may also exist extracellularly as a result of cellular apoptosis, necrosis, or through the action of specific secretory pathways (146). Experiments performed by the selective mutation of secretory signals contained in the carboxy-terminal region of Tax, and evidence collected from the interaction of Tax with various secretory proteins, have elucidated the secretory pathway of Tax from the nucleus into the extra-cellular environment. Tax enters the secretory pathway by a leaderless system, and is secreted from cells in the regulated secretory pathway initiating in the nucleus, and in the cytoplasm traveling to the endoplasmic reticulum, golgi, post-golgi, and lastly exiting the plasma membrane (147). Extracellular Tax contributes to the hyperimmune and inflammatory response observed during the course of HAM/TSP by its transcriptional effects on neighboring cells, stimulation of immune response, and its role as an extracellular cytokine. It has also been demonstrated to accumulate in the peripheral blood and the CNS of HAM/TSP patients (42). Extracellular Tax has been shown to induce the production of TNF-α from a human neuronal cell line at a concentration that has been shown to be produced by HTLV-1-infected cells (88, 148). Release of TNF-α may result in both an autocrine and paracrine cytokine-mediated destruction of neuronal tissue. Other pathologic processes observed in HAM/TSP patients include demyelination of CNS neurons, which may also be a direct effect of extracellular Tax (88, 92). In addition to neurons, adult human microglial cells were also shown to secrete TNF-α, IL-1β, and IL-6 in response to Tax (70). These observations correlate with additional studies

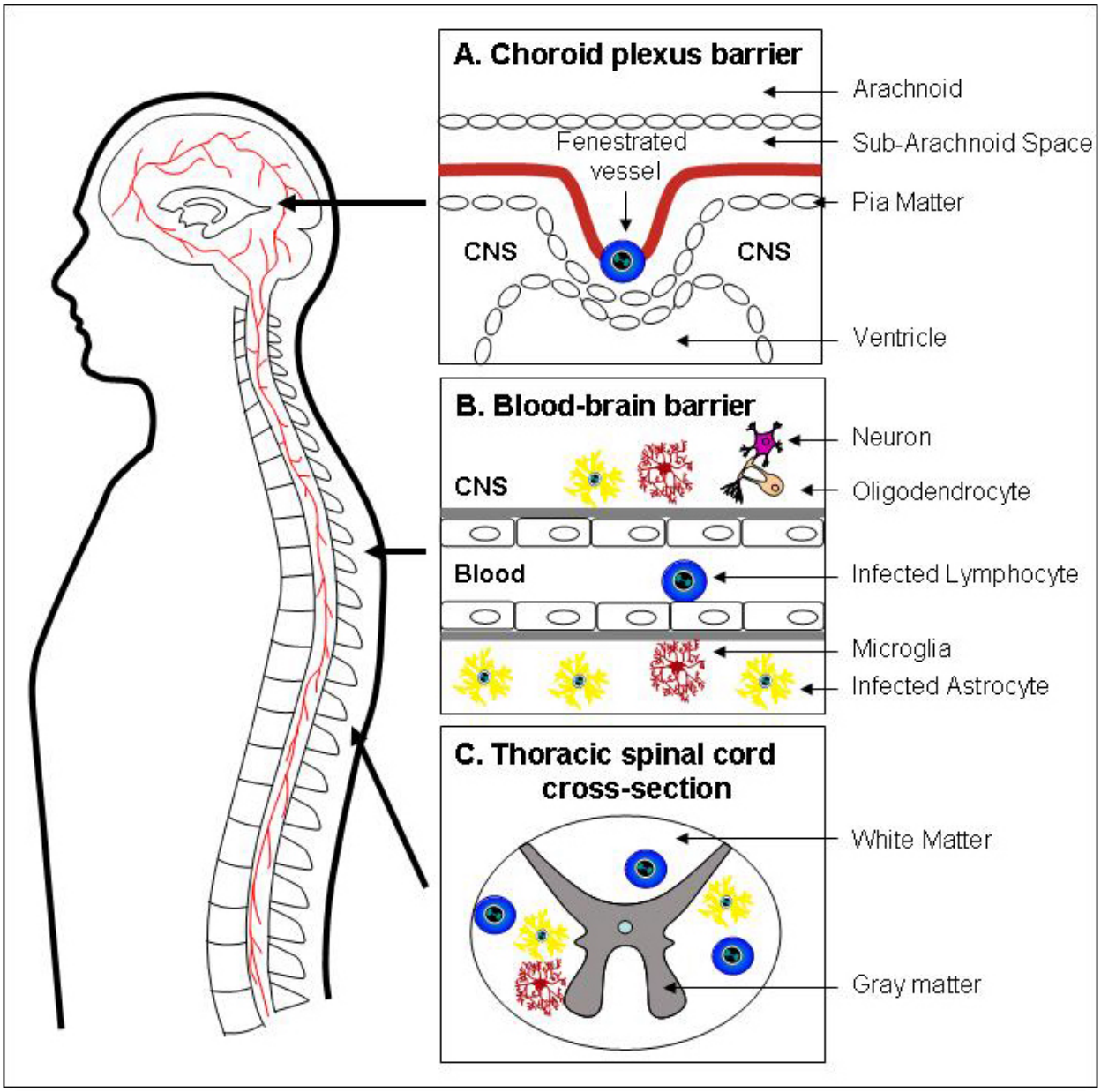

Figure 2. Areas of lymphocyte migration. (A) Regulatory lymphocytes and HTLV-1-infected lymphocytes may gain entry into the CNS through the choroid plexus BBB interface. The vesicles in the subarachnoid space are fenestrated, therefore lymphocytes are found to aggregate in this space. (B) Activated, HTLV-1-infected lymphocytes may gain entry to the CNS through the BBB and aggregate at the perivascular space. (C) Representation of a cross-section of the thoracic spinal cord. Lymphocytes infiltrate the thoracic spinal cord at areas of inflammation and demyelination, localized to the lateral areas near the corticospinal tract.

demonstrating that HTLV-1-infected microglial cells secrete both TNF-α and IL-6 but not IL-1β, suggesting that Tax may have a paracrine effect on other Tax-producing cells (70). The effects of extracellular Tax have not been limited to the CNS, primary human peripheral blood macrophages have also been shown to secrete TNF-α, IL-1, and IL-6 in response to extracellular Tax (70). Recently, cell-free Tax has been demonstrated in the CSF of HAM/TSP patients (42) indicating that Tax is available for immune recognition by APCs. Extracellular Tax released from Tax-producing cells by secretion or apoptosis and necrosis may be internalized by professional antigen presenting cells (APCs). Tax peptides presented in the context of MHC by APCs would result in lysis of Tax-expressing cells by Tax-specific $CD8^+$ T cells. Either production of toxic molecules or specific cell lysis could result in significant CNS damage similar to that observed in HAM/TSP.

6. INTERMEDIATE FACTORS

6.1. Blood-brain barrier

The BBB is a tightly controlled barrier separating the circulating blood flow from the parenchyma, and is composed of three main components: a basement membrane including pericytes (a cell population which resides in the basement membrane and stabilizes blood vessel formation), specialized endothelial cells, and astrocytes (149). In order to access the BBB, leukocytes must migrate through the internal carotid arteries passing through the BBB (150). The receptor interactions of lymphocyte function-associated antigen (LFA)-1, ICAM-1, VCAM-1, and very late antigen (VLA)-4 mediate leukocyte migration through the BBB (150, 151). As part of the BBB, the blood-CSF barrier is situated in the ventricles at the site of the choroid plexus, the area that is responsible for generating the CSF. The ventricles open to the subarachnoid space, and the CSF generated is released into this space surrounding the CNS. Infiltrating leukocytes traverse the blood into the choroid plexus, and then follow the path of the CSF. The cells that cross the blood-CSF barrier are predominantly $CD4^+$ T cells expressing characteristics of central memory T cells, although other lymphocytes such as CTLs also gain entry to the CNS through the internal carotid artery to the subarachnoid space, again coming in contact with the CSF (150). HTLV-1-infected lymphocytes aggregate in CNS regions such as the periventricular areas of the blood-CSF barrier, the subarachnoid space, and the thoracic and lumbar regions of the spinal cord (Figure 2).

It is thought that a small number of T lymphocyte cells patrol the CNS under normal healthy circumstances under tight immunologic control. If no antigen is encountered during surveillance, these T cells do not remain in the CNS (152). However, in inflammatory situations with the accompanying breakdown of the BBB, a large number of leukocytes are able to gain access. Experiments performed utilizing both the HTLV-1-producing T cell line, MT2, and endothelial cells containing CNS barrier characteristics have examined the mechanisms of viral infiltration into the CNS. In this model, it was found that the HTLV-1-infected MT2 cells have a greater ability to adhere to and migrate through the endothelial layer than the uninfected control lymphocytes; LFA-1, ICAM-1, and VCAM-1 molecules were also found to be upregulated (151).

6.2. Proinflammatory cytokines/chemokines

Cytokines and chemokines function as important signaling factors in the healthy CNS, but a severe disruption has been postulated to contribute to the dysfunctional host-viral immune function and pathogenesis that occurs in inflammatory diseases such as HAM/TSP. Elevated levels of the proinflammatory cytokines IFN-γ, TNF-α, IL-1, IL-6, and GM-CSF are found in the CSF of HAM/TSP patients (153-157). CTL cells are important in the reduction of the proviral load in HTLV-1-infected patients, but in patients with HAM/TSP, the amount of antigen available may be at such a level that a threshold is crossed and CTL cells are stimulated to release proinflammatory cytokines such as IFN-γ and TNF-α (46, 158, 159). Polymorphism experiments performed by Vine and Bangham (160) have recently found an association suggesting a link between the TNF-α promoter gene allele (TNF-863A) and the risk for HAM/TSP provided an individual possessed a high proviral load (160). An association between the TNF-863A allele and the HTLV-1-associated inflammatory syndrome, uveitis, has previously been established (161). Furthermore, within the same polymorphism study, other allele associations were identified as well, including a correlation with allele IL-15 +191C with respect to reducing proviral load in HTLV-1-infected HAM/TSP patients (160). As previously discussed, many of the resident CNS cells will also release cytokines when induced by extracellular Tax. The chemokines, monokine-induced by interferon-γ (MIG) and IP-10, associated with recruitment of Th1-associated lymphocytes, have been shown to be present in high levels in the serum, and positively correlate with the level of IFN-γ in HAM/TSP patients, when HAM/TSP and HTLV-1-infected asymptomatic carriers were measured as an associated group (162).

6.3. Infiltrating blood cells

Peripheral and CNS inflammation differ, in that in the CNS, lymphocyte cell infiltration is not immediate, but a delayed phenomena requiring a matter of days (64, 163, 164). Following recruitment, most lymphocytes do not directly enter the CNS parenchyma until the end stages of disease, but instead accumulate in perivascular regions, the ventricles, and under the meninges (62, 165-171). The phenotype of infiltrating lymphocytes is determined by the stage of HAM/TSP (41). During the primary stages of the disease, $CD4^+$ T cells, B lymphocytes, and $CD8^+$ T cells infiltrate the CNS in relatively equal numbers. The later stages of the disease are marked by the predominance of $CD8^+$ T cells largely specific for Tax, circulating within the CNS, predominantly in the subarachnoid space and parenchyma (27, 34). Recently, APCs have been identified in the CNS, either as resident cells such as microglia, or as monocytes or DCs that have traversed the BBB. Parenchymal microglia may be induced to differentiate in the presence of GM-CSF and M-CSF and acquire characteristics of immature DCs (59). There are three areas where T cells may encounter APCs, the systemic immune compartment with its secondary lymphoid tissues, the CNS parenchyma with microglia and astrocytes, and the perivascular menigeal space with macrophages and DCs (172). DCs are the most potent APCs, capable of stimulating both naïve $CD4^+$ Tcells and $CD8^+$ T cells (97). It has been postulated that DCs may be recruited into the choroid plexus or lesion sites of the inflammatory CNS model by cytokines released from injured CNS tissue, such as GM-CSF, TNF-α, and IL-1 (173). Two subsets of DCs have been identified in humans, myeloid DCs, and lymphoid or plasmacytoid DCs. Myeloid DCs are preferentially localized to skin and mucosal tissues, and plasmacytoid DCs preferentially in the peripheral blood (174). Both subsets were found to be present in the CSF under healthy conditions, but are found in higher concentrations in inflammatory neurologic disorders (175). Myeloid DCs appear better able to

stimulate $CD4^+$ and $CD8^+$ T cells and a Th1 response, and plasmacytoid DCs preferentially stimulate a Th2 response. HAM/TSP is predominantly a Th1-driven response while ATL is predominantly a Th2/Th3 response. Therefore, it has been proposed that myeloid DCs are preferentially infected by HTLV-1 in individuals that progress to HAM/TSP and plasmacytoid DCs are infected in individuals that develop ATL (17). DCs are implicated to play a role in the pathogenesis of HAM/TSP by the presentation of Tax to naïve $CD8^+$ T cells by infected DCs, thereby activating and inducing a Tax-specific CTL response (17, 97). Infected DCs are not necessarily the primary DCs encountered, other factors are involved. Experiments performed in our laboratory have demonstrated that DCs pulsed with Tax secrete cytokines and chemokines as determined by cytokine array. These cytokines and chemokines include the Th1 cytokines, IFN-γ, IL-12, and TNF-α and the C-C chemokines eotaxin, MCP-1, and MCP-3, all released in significantly high amounts garnering at least a 2-fold increase. This Tax-induced cytokine secretion may contribute to the cellular activation and tissue damage characteristic of HAM/TSP (176). Additionally, the exposure of DCs to Tax has like-wise been found to activate DCs and increase expression of CD60 and CD86 mRNA (177).

7. CONCLUSIONS AND FUTURE PERSPECTIVES

The CNS is a specialized site with limited communication between the peripheral blood immune system and its own. The capability of the CNS and the extent of the roles of individual CNS resident cells in viral and immune reactions have not been fully delineated, especially with regard to HAM/TSP. Currently, therapies to treat symptoms involve the use of steroids to control the overly active immune response while nucleoside analog reverse-transcriptase inhibitors have been shown to successfully decrease HTLV-1 proviral load. HIV-1 protease inhibitors have been tested on HTLV-1 as well, but were shown to be less effective due to variations in the HTLV-1 Gag protein (178-180). Highly active antiretroviral therapy (HAART) remains a first line of defense against retroviruses such as HIV-1, however, it is less effective in treating retroviral neurological disorders as it is not able to easily cross the BBB, so a viral reservoir remains in the CNS (181). Insights gained into the viral CNS cellular infection have predominantly been the result of experiments performed involving the *in vitro* infection of individual cell populations and *in situ* hybridization of CNS tissue. *In vitro* experiments may contribute insights but are inherently physiologically limited. The resident CNS cell populations represent a highly complex interactive compartment, thus an *in vivo* model would be much more useful in understanding the pathophysiology of HAM/TSP and associated neurologic disorders. We are currently working on the development of a transgenic mouse (C57BL/6-Tg (HLA-A2.1) model with chimeric HTLV-1 for HAM/TSP mimicking human neurologic demyelination and neuroinflammatory disorders similar to multiple sclerosis. Further research is warranted to develop a useful small animal model that could be exploited as a tool for screening and evaluation of anti-HTLV-1 molecules for improved therapy.

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Send correspondence to: Zafar K. Khan, Department of Microbiology and Immunology, and Center for Molecular Virology and Neuroimmunology, Center for Cancer Biology, Institute for Molecular Medicine & Infectious Disease, Drexel University College of Medicine, 245N, 15th St., 18th Floor, Philadelphia PA 19102, Tel: 215-762-3719, Fax: 215-762-1955, E-mail: zkhan@drexelmed.edu

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