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MINIREVIEW

Lentiviral Neuropathogenesis: Comparative Neuroinvasion, Neurotropism, Neurovirulence, and Host Neurosusceptibility

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Despite extensive genetic diversity among lentiviruses, they share many biological properties, including similar structural and genomic organizations, Mg^{2+}-dependent reverse transcriptase activity, and broad cellular tropisms involving both proliferating and nonproliferating cells within and outside the nervous system (30). Lentiviruses can also be subdivided on the basis of pathogenesis into peripheral immune deficiency-inducing viruses, such as human (HIV), simian (SIV), feline (FIV), bovine (BIV), and chimeric simian-human (SHIV) immunodeficiency viruses, and those that are immune activators, including caprine arthritis encephalitis virus (CAEV), maedivisna virus (MVV), and equine infectious anemia virus (EIAV) (Table 1). Systemically, most lentiviruses exhibit a distinct disease pattern in which primary infection induces acute disease and an intense immune response, followed by a lengthy period of subclinical infection (lenti = slow) and a terminal phase resulting in death (22). Immunodeficiency-associated lentiviral infections usually trigger a robust host immune response that is diminished over time, permitting opportunistic infections. In contrast, infections by the immune-activating lentiviruses are characterized by a terminal phase of host immune activation. CAEV and MVV infections are manifested as systemic inflammation with chronic arthritis, pneumonia, and mastitis, while EIAV induces recurrent episodes of an autoimmune-mediated acute hemolytic disease (17, 57, 89).

In contrast to the distinct differences in peripheral immune responses, both lentiviral groups exhibit immune dysregulation in the central nervous system (CNS), defined by inflammation and neuronal injury. Moreover, the ability to infect and replicate in cells of monocyte/macrophage lineage is common to all lentiviruses. Among the immunodeficiency viruses, which recapitulate many of the neurobehavioral and neuropathological features of HIV type 1 (HIV-1)-induced neurological disease, primary lentivirus-induced neurological disease occurs more frequently with advancing immune suppression (84, 92, 102). The frequency of neuropathological changes induced in FIV- and SIV-infected cats and monkeys, respectively, varies depending on the viral strain and host-specific factors. FIV-induced brain disease occurs in 20 to 50% of infected animals, usually concurrent with depressed CD4 T-lymphocyte levels (98), and may manifest as psychomotor slowing, altered sleep patterns, ataxia, seizures, and electrophysiological abnormalities (32, 55, 96–98). The behavioral abnormalities are often accompanied by neuropathological changes, such as perivascular infiltration, gliosis, microglial nodules, myelin pallor, meningitis, rare multinucleated giant cells, and progressive neuronal loss within the brain (11, 32, 96, 104, 107). SIV infection may also result in cognitive and motor impairment (90), with approximately 50% of infected macaques exhibiting neuropathological changes, including SIV encephalitis (SIV-E) (126), which includes multinucleated giant cells and perivascular cuffing together with neuronal damage, microglial nodules, gliosis, and an abnormal blood-brain barrier (22, 57, 70, 78). Importantly, SIV antigen has been identified within these brain lesions (125). The pathological changes observed in SHIV-infected animals can resemble those observed during SIV infection (106). BIV-infected cattle may exhibit immune suppression (132) and encephalitis (50, 117), characterized by leukocyte infiltration of the perivascular spaces, parenchyma, and meninges (117).

Among CAEV- and MVV-infected animals, neurological disease can manifest as tremor, blindness, ataxia, and hind limb weakness that lead to paralysis and death (22, 57, 64). Neuropathological lesions predominate in the white matter of the spinal cord and brain, with perivascular cuffing, lymphocyte and monocyte infiltration, meningoencephalitis, glial nodules, astrocytosis, and demyelination reported (57, 64, 92, 107). In some EIAV-infected animals neurobehavioral features, such as psychomotor slowing and ataxia, occur and are accompanied by granulomatous ependymitis, encephalitis and meningitis, gliosis, and perivascular cuffing (18, 57, 64, 87). Despite the presence of neurological disease (57, 107), immune activation without subsequent suppression is the key feature of systemic immunity among this group of viruses.

The specific neuropathogenic mechanisms underlying lentiviral infections of the nervous system can be defined by viral neuroinvasive, neurotropic, and neurovirulent properties, together with individual host neurosusceptibility (Table 1) (57, 101). Below we address these properties in detail, with an emphasis on two animal models for HIV-induced neurological disease, SIV and FIV.

NEUROINVASION

Neuroinvasion, the ability of lentiviruses to enter the CNS, is required for the development of neurological disease. Several reports have demonstrated that lentiviruses colonize the ner-

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TABLE 1. Characteristics of lentiviral neuropathogenesis[a]

Virus	Genome size (kb)	Peripheral tropism	CNS tropism[b]	Receptors[c]	Neuropathology	Neuropathogenesis		References
						Viral factors	Host factors[d]	
SIV	9.6	$CD4^+$ T lymphocyte, macrophage	Macrophage, microglia	**CD4, CCR2b, CCR5**, CCR8, APJ, RDC1, Gpr1, Gpr15, STRL33, Chem R23	Perivascular cuffing, demyelination, multinucleated giant cells, glial nodules, neuronal damage or loss, abnormal blood-brain barrier	Strain specificity; *env*, *nef*, 3′ LTR polymorphism	CTL, cytokines, chemokines, neuronal cell cycle regulators, calbindin-D-28K, NO, iNOS, host species, host age, systemic immune suppression	5, 10, 22, 28, 30, 36, 39, 41, 57, 63, 71, 76, 77, 81, 83, 107, 112, 114
FIV	9.5	$CD4^+$ T lymphocyte, B cell, macrophage	Macrophage, microglia	**CXCR4**, heparans, CCR3, CCR5	Perivascular infiltration, gliosis, glial nodules, myelin pallor, meningitis, vacuolar myelopathy, neuronal loss	Strain specificity; *env* polymorphism	Glutamate, TNF-α, MMPs, host age, host sex, coinfection, systemic immune suppression	22, 29, 30, 46, 57, 59, 60, 100, 102, 104, 107
BIV	8.5	$CD4^+$ T lymphocyte, B cell, macrophage	Unknown	Unknown	Encephalitis, infiltration of lymphocytes, monocytes, and plasma cells	Strain specificity	Unknown	30, 50, 57, 128
HIV-1	9.2	$CD4^+$ T lymphocyte, macrophage	Macrophage, microglia	**CD4, CCR5, CXCR4**, CCR2b, CCR3, CCR8, APJ	Multinucleated giant cells, myelin pallor, perivascular cuffing, glial nodules, abnormal blood-brain barrier	*env, tat* polymorphisms; *vpr, nef*	Host age and genetic variation, systemic immune suppression, cytokines, chemokines, free radicals, MMPs	22, 30, 41, 57, 62, 107
HIV-2	10.4	$CD4^+$ T lymphocyte, macrophage	Macrophage, microglia	**CD4, CCR5, CXCR4**, CCR2b, CX3CR1, APJ, GPR15, Chem R23, STRL33, CCR8	Multinucleated giant cells	Unknown	Unknown	22, 30, 41, 57, 79, 110
MVV	9.2	Macrophage	Macrophage, microglia	Unknown	Perivascular cuffing, lymphocyte and monocyte infiltration, meningoencephalitis, glial nodules, astrocytosis, demyelination	U3-LTR, *tat*	Cytokines, up-regulated MHC class II, host age and breed	6, 22, 24, 30, 33, 57, 64, 92, 107, 118
CAEV	9.2	Macrophage	Macrophage, microglia	Unknown	Perivascular cuffing, lymphocyte and monocyte infiltration, meningoencephalitis, glial nodules, astrocytosis, demyelination	Unknown	Host age	22, 30, 57, 64
EIAV	8.4	Macrophage	Macrophage, microglia	Unknown	Granulomatous ependymitis, encephalitis, gliosis, meningitis, perivascular cuffing	*env*	Unknown	22, 30, 57, 64, 66

[a] Adapted from reference 57.
[b] Principal cell type infected.
[c] Principal in vivo receptors are shown in boldface.
[d] CTL, cytotoxic T lymphocyte; iNOs, inducible nitric oxide synthase; MMP, matrix metalloproteinase; MHC, major histocompatibility complex.

vous system soon after infection (26, 100, 109), although the proposed mechanisms by which lentiviruses traverse the blood-brain barrier are diverse, including direct infection of endothelial cells and subsequent release of virus into the brain, infection of the choroid plexus, or trafficking into the CNS of infected hematogenous cells, such as monocytes and lymphocytes (42, 135). Reports suggest that peripheral T-lymphocyte activation, such as by viral infection, facilitates leukocyte entry into the brain parenchyma (53, 116, 131). Moreover, individual lentiviruses may employ more than one route of brain entry.

Among the immunodeficiency viruses, SIV typifies the diversity of mechanisms that may be employed by lentiviruses. The association of SIV RNA with brain capillary endothelial cells in vivo suggests that infection of these cells may facilitate entry into the brain (82, 135), directed by the viral envelope protein (8). In addition, SIV-infected monocytes recruited across the blood-brain barrier differentiate into perivascular macrophages and may promote invasion of the CNS (71). The choroid plexus, which may also provide a portal for HIV-1 (8, 19), has been proposed as a route of CNS entry for SIV based on the ability to detect SIV antigen and RNA within this region (70, 72). In advanced SIV-E, disruption of tight junctions between brain endothelial cells is reported in combination with an accumulation of perivascular macrophages (78, 135) and may be an alternative mechanism for neuroinvasion. FIV also appears to penetrate the blood-brain barrier by direct infection of endothelial cells, a route supported by reports that the virus can infect primary brain microvessel endothelial cultures (119) and the presence of the putative FIV receptor, CXCR4, on endothelium (68). As with the primate lentiviruses, infected leukocytes also serve as vehicles for FIV entry into the brain (51).

Like the primate lentiviruses, detection of CAEV proviral *pol* sequences in choroid plexus tissue has implicated this route of neuroinvasion (70, 72, 108). The mechanism of MVV neuroinvasion proposed by Chebloune et al. (16), however, suggests that activated T cells may migrate to the brain and provide chemotactic stimuli to recruit infected monocytes to the CNS (16, 94). Intracerebral inoculation of a neuroadapted MVV strain results in replication in the brain and induces encephalitis; however, bone marrow inoculation of the same virus fails to induce encephalitis (24), indicating that neuroinvasion and neurovirulence are discrete viral properties.

NEUROTROPISM

Neurotropism, broadly defined as the ability to infect cells within the nervous system, is determined in part by the individual cell types permissive to viral entry and replication, expression of receptor molecules that allow viral entry, and the specific strain of the infecting virus. A common feature of all lentiviruses is their ability to infect CNS cells of differentiated monocyte/macrophage (and microglial) lineage (22, 92). The immunodeficiency lentiviruses, including SHIV, in which the SIV envelope gene has been replaced with the HIV-1 counterpart (15, 56, 75, 80), readily infect both peripheral T lymphocytes and monocytoid cells in the periphery (22, 57). Within the CNS, however, lentiviral replication occurs predominantly within macrophages and microglia. Recent reports suggest that perivascular macrophages, but not parenchymal microglia, are the principal CNS cell type productively infected by SIV (130) and HIV (37). In contrast, immune-activating lentiviruses are predominately monocyte/macrophage-tropic within the CNS and the periphery (22, 33, 57). Of note is the finding that EIAV, MVV, and CAEV replication in the nervous system is accompanied by an extensive inflammatory response (22, 33, 57), possibly reflecting the infection and activation of cells of monocyte and macrophage lineage. Although perivascular macrophages and microglia are the major cell types in the brain infected by lentiviruses, persistent infection accompanied by restricted replication and antigen expression has been reported for other host cells. There is also convincing evidence for in vivo and in vitro infection of astrocytes with limited replication by CAEV (108), FIV (31), SIV (47), and HIV (7). In vitro and in vivo infection of brain endothelial cells by MVV (43), FIV (119), HIV (7), and SIV (82) has been reported, although in vivo infection has been shown chiefly in SIV infection. Neuronotropism, or the ability to infect neurons, has been shown in vitro and possibly in vivo for HIV (122), although the pathogenic significance of neuronal infection remains uncertain. Oligodendrocytes have been shown to be infected by CAEV but not by other lentiviruses (108).

The receptor mechanisms that facilitate lentiviral entry of brain cells are incompletely elucidated. CD4, the primary receptor for most of the primate lentiviruses (HIV, SIV, and SHIV) is expressed in the nervous system and acts in conjunction with several G-coupled seven-transmembrane-spanning chemokine receptors to permit cell entry (Table 1). Although chemokine receptors are associated primarily with immune cell trafficking, many are also expressed in a range of neural cell types, including perivascular macrophages, resident microglia, neuronal subpopulations, and astrocytes (41, 52, 67). HIV-1 macrophage or T-lymphocyte tropism is largely correlated with CCR5 and CXCR4 coreceptor usage, respectively (41). In addition, dualtropic HIV-1, capable of using either CXCR4 or CCR5 as a coreceptor, and viruses that utilize other coreceptors, albeit with reduced efficiency, have also been reported (45). In contrast, the primary receptor facilitating SIV entry may depend on the individual viral strain. SIV may employ CD4 together with CCR5 as a coreceptor to infect both macrophages and lymphocytes (20, 83), possibly through determinants in the SIV envelope that interact with alternate portions of CCR5 to direct cell-specific tropism (35). However, SIV may also enter CD4-negative cells, such as brain capillary endothelial cells, by exploiting CCR5 as its primary receptor in a CD4-independent manner (34, 35, 83). Similar to HIV-1, some chimeric SHIV isolates may use both CXCR4 and CCR5 as coreceptors (15). In the periphery, HIV-1 infection remains CD4 dependent; however, a number of HIV-1 brain-derived isolates exhibit a reduced dependence on CD4 for viral entry (45, 113).

The primary receptors utilized by the nonprimate lentiviruses, particularly BIV, MVV, CAEV, and EIAV, are less clearly elucidated. However, several chemokine receptors have been implicated in FIV infection, making it the only nonprimate lentivirus known to employ these receptors for cell recognition. For example, FIV has been shown to use the feline CXCR4 receptor, but not feline CD4, for infection (99, 129), and entry can be blocked by the natural CXCR4 ligand, stromal cell-derived factor 1 (29, 54). Direct or indirect interac-

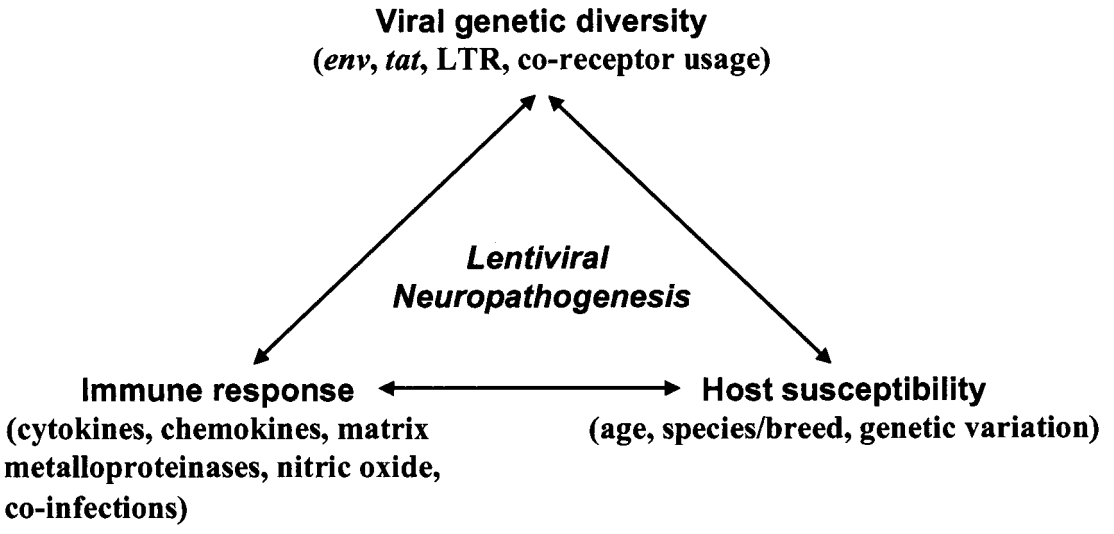

FIG. 1. Determinants of lentiviral neuropathogenesis.

tions between FIV and CXCR4 may have a role in pathogenicity as well as tropism, since CXCR4 is expressed on cat neurons, astrocytes, and brain endothelial cells (68, 91). Recent evidence also suggests that FIV might use CCR3 and CCR5 for infection through a mechanism that is viral strain specific and dependent on envelope sequence (59, 61, 74). The FIV envelope surface unit can also engage in nonchemokine receptor interactions, and cell surface heparans may have a role in binding (29).

In addition to the elements that mediate cell recognition and entry, such as the presence of receptors, postentry factors also contribute to neurotropism. For example, the sequence of the MVV (2) long terminal repeat (LTR) has been shown to influence neural cytotropism. Thus, following CNS invasion and entry of susceptible cells, both viral and host-specific factors direct neurological disease development.

NEUROVIRULENCE

Neurovirulence, or the capacity of viruses to cause disease within the nervous system, involves both host- and virus-specific factors (Fig. 1). The lentiviruses represent unique neurovirulence mechanisms because of the systemic immune abnormalities that accompany the direct nervous system effects of these viruses. This is most apparent in the CNS due to its relative immune-privileged status (120).

Viral properties. Viral genetic diversity is an important determinant of neuropathogenesis and evasion of the host immune response. SIV strain specificity can dictate the ability to replicate within microglia and the severity of the neurological lesions and signs that develop following colonization of the nervous system (27). Similarly, FIV neurovirulence is reported to be strain specific and is associated with the development of systemic immune suppression (60, 62, 102). Furthermore, specific HIV-1 sequences are correlated with variable disease progression (reviewed in reference 103). Thus, variation at the nucleotide and protein levels in specific viral genes is an important determinant of lentivirus-induced disease (Fig. 1).

The lentivirus envelope protein surface unit (SU) and transmembrane unit (TM) have the potential to mediate neuropathogenesis through direct or indirect mechanisms (Table 1). The use of SIV chimeras that express sequences from a macrophagetropic neurovirulent SIV clone in a lymphocytetropic and nonneurovirulent SIV background identified the SU (gp120) and short TM segment (gp41) as the determinants for macrophage tropism, whereas the complete *env*, *nef*, and 3′ LTR contiguous sequences are required for neurovirulence (81). Moreover, full-length *nef* sequences and variation in the TM portion of *env* are associated with increased replication in the CNS (38), and application of recombinant SIV gp120 to cultured macaque neurons results in a calcium flux that may reflect neuronal dysfunction in vivo (67). A SHIV mutant that lacks most of the *vpu* gene is nonpathogenic in pig-tailed macaques, whereas compensatory mutations in gp120 and Nef proteins are associated with the development of systemic and neurological disease (115). Similarly, diversity in the viral envelope influences the ability of neurovirulent and nonneurovirulent FIV isolates to modulate the activity of intracellular signaling pathways and alter the expression of molecules that may have a role in CNS damage, such as matrix metalloproteinases (60, 62). Full-length FIV envelope protein may induce neuronal injury through excitotoxic mechanisms, as exposure of neuronal cultures to neurovirulent FIV particles or purified *env*-encoded proteins alters intracellular calcium signaling (46). MVV *env* and U3-LTR sequence diversity may influence disease, as molecular variation between isolates that induce pneumonia (maedi variant) and those that result in encephalitis (visna variant) was identified (6).

Other viral proteins may act cooperatively with the envelope proteins to induce lentiviral brain disease, including the transactivator protein, Tat, which has been implicated in the neurological disease caused by HIV-1 (21) and in other lentiviruses. MVV Tat induces death in neuronal cultures and correlates with increased intracellular calcium levels (121), similar to reports on HIV-1 Tat (93). Intrastriatal injection of the MVV Tat basic domain in rats is associated with acute

neurotoxicity and can be modulated by an *N*-methyl-*O*-aspartate receptor antagonist (118). In contrast, the dUTPase accessory protein, encoded by nonprimate lentiviruses, is not involved in MVV neuropathogenesis, as a dUTPase-deficient MVV mutant inoculated intracerebrally remained neuropathogenic (95).

The association between viral load and the development of neurological disease has remained controversial (58, 86). Several reports propose a correlation between HIV and SIV viral RNA, provirus, or antigen levels in the CNS and neurological impairment (13, 27, 136). In contrast, evidence that a discrepancy between HIV, SIV, FIV, and MVV viral load (as measured by viral antigen and/or RNA) and the development and severity of neurological disease exists, suggesting that other viral properties and host factors are involved in neuropathogenesis (11, 27, 43, 85). These conflicting reports suggest that a more detailed examination of viral load and neurological disease is required.

Host response and mediator molecules. To date, lentivirus-induced neuropathogenesis is defined predominately by innate immune responses (4) (Fig. 1). However, adaptive cellular immunity may have a role in neurological disease, as SIV-infected monkey brains harbor increased levels of activated cytotoxic T lymphocytes (39, 124), while humoral immunity's contribution to neuropathogenesis remains uncertain. SIV neuropathogenesis is mediated in a large part by innate immune cells, including microglia and astrocytes. These cells are the principal cytokine producers of the brain, and increased levels of cytokines (interleukin-1β, tumor necrosis factor alpha [TNF-α], and gamma interferon) and chemokines (MIP-1α, MIP-1β, RANTES, MCP-3, and IP-10) are associated with SIV-E. This suggests that SIV infection of the CNS promotes increases in these proinflammatory molecules, which may recruit pathogenic inflammatory macrophage cells into the CNS (67, 73, 107, 111). These chemokines may also directly interact with chemokine receptors present on feline and macaque astrocytes and neurons to produce toxic effects (40, 67, 68, 88, 133). SIV infection may also promote neuropathogenesis through induction of neuronal cell cycle regulators such as elevated expression of the tumor suppressor p53 and the transcriptional activator E2F1 (63). An excitotoxic mechanism of neuronal damage is also postulated, as SIV activation of astrocytes results in increased expression of calbindin-D-28k, a calcium binding protein that is up-regulated during excitotoxicity (10). Nitric oxide and cytokine-inducible nitric oxide synthase are also proposed to mediate CNS injury in SIV-infected macaques (73, 76). Dysfunction in specific neuronal populations, such as somatostatinergic interneurons, may be involved in SIV-induced neurologic disease, as SIV-infected macaques have an increased number of interneurons positive for preprosomatostatin mRNA, which correlates with motor and cognitive abnormalities (25).

Similarly, FIV-related CNS injury might be mediated, in part, by the CNS innate immunity, driven by viral infection and altered expression of host cell molecules (107). Brain samples from animals infected with a neurovirulent FIV strain exhibited increased TNF-α and matrix metalloproteinase-2 expression compared to those from animals infected with nonneurovirulent strains (60), similar to findings for HIV infection. FIV infections also result in activation of microglia and astrocytes with accompanying neuronal loss (104). Excitoxicity may lead to neuronal death in FIV-infected animals, as increased glutamate levels and decreased glutamate decarboxylase levels were detected in the frontal cortex (104). Furthermore, TNF-α may have a role in neuropathogenesis, as early after infection increased CNS viral loads are correlated with up-regulated TNF-α expression in the brain (100).

Like for the immunodeficiency lentiviruses, an increased CNS inflammatory response elicited by the immune-activating lentiviruses is well established. MVV-associated neuropathology is defined by increased proinflammatory cytokine expression produced as a consequence of viral infection, as indicated by infection of ovine microglial cells resulting in increased levels of TNF-α and interleukin-6 mRNAs (33). In addition, brain tissue from MVV-infected sheep exhibits up-regulated major histocompatibility complex class II expression and perivascular macrophage production of TNF-α, which may contribute to neuropathology (24). Similarly, increased cell death was reported for CAEV-infected primary microglial cultures, while supernatants from infected microglia or mixed glial cultures induced death in 50% of cultured neurons (1).

NEUROSUSCEPTIBILITY

Neurosusceptibility refers to the host's vulnerability to virus-induced neurological disease and is dictated by host age, species, immune status, and genetic background (Fig. 1). For example, the development of HIV-associated dementia is more frequent at the extremes of age and has also been associated with genetic variation in the CCR5, TNF-α, and APOE genes (12, 23, 105, 123). Similarly, SIV infection of nonhuman African primates occurs naturally and is nonpathogenic, whereas cross-species transmission to wild Asian macaques, which are not normally infected with SIV, induces simian AIDS and encephalitis (reviewed in references 22, 57, and 107). Viral DNA (cerebellum), RNA (CSF), and antigen (cerebrum and CSF) were detected in healthy African green monkeys naturally infected with SIV (14), and thus the absence of neurological disease is not attributable to the absence of neuroinvasiveness or neurotropism. Similar to the case for HIV, host age may influence SIV and FIV pathogenesis, in which young animals are more susceptible to CNS disease (102, 112). Moreover, systemic immune suppression was correlated with neurovirulence, indicating that systemic factors influence neuropathogenesis (127). In the terminal stages of FIV, SIV, BIV, and HIV infections, systemic immune deficiency, defined by a progressive loss of $CD4^+$ T cells, opportunistic infections, and CNS complications, develops (55, 102, 107, 117). As described above, SIV, FIV, and HIV replication in the CNS and neurological disease can occur early after infection but is usually identified after the onset of AIDS (102, 130), and reports suggest that the development of FIV- and SIV-induced neurological lesions is associated with host immune suppression (102, 134). FIV infection is also more prevalent in a subset of the cat population, with older, male, free-roaming cats most commonly affected (57, 64). Moreover, coinfection with feline leukemia virus or feline peritonitis virus exacerbates the severity of FIV neuropathology (55). Thus, host genetic susceptibility influences the development of lentiviral neuropathogenesis,

but systemic immune suppression is also correlated with the occurrence of neurological disease.

The development and severity of MVV- and CAEV-induced encephalitis are dependent on host factors such as age and breed. CNS disease occurs more frequently in newborn goats (CAEV) (64); conversely, clinical disease rarely develops in sheep (MVV) that are less than 2 years of age (57). MVV-infected Icelandic or milk-producing sheep are more likely to develop neurological complications than American meat- and wool-type breeds or European flocks (64, 65, 92). In one study, viral replication was identified predominantly in the lungs of British sheep inoculated intracranially with neurovirulent and nonneurovirulent strains of MVV, whereas replication was found in the lungs and brains of Icelandic sheep (65). This suggests that genetic factors involved in systemic MVV disease are unique from those involved in the development of encephalitis (65). MVV, CAEV, and EIAV systemic disease is not characterized by terminal immune suppression, and unlike for the immunodeficiency lentiviruses, a direct relationship between systemic disease and the development of neurological disease has not been identified.

FUTURE PERSPECTIVES

Lentiviral neuropathogenesis reflects a series of complex interactions between the virus and host that include viral genetic diversity, host immune response, and genetic susceptibility (Fig. 1). Future studies are likely to delineate new relationships between virus and host, including the roles of select host genetic susceptibilities and the exact mechanisms by which the wide spectrum of host mediator molecules cause brain damage. Nonetheless, nonhuman lentiviruses as models for HIV-induced neurological disease have a number of limitations. CAEV, MVV, and EIAV fail to induce systemic immune suppression, an invariable aspect of HIV-1 infection, and thus the nonhuman immunodeficiency viruses more accurately reflect HIV-1 infection. However, the receptor usage and broader cell tropism of FIV, or the absence of AIDS in the natural hosts of SIV and the extremely rapid disease progression that occurs in some susceptible macaques, are important differences from HIV-1-induced disease. Despite these obstacles, SIV and FIV share many common features with HIV and serve as the most relevant models for HIV-induced neurological disease. Moreover, these animal models allow for in vivo investigations that cannot be evaluated in human models, including characterization of the simultaneous relationship(s) between failing systemic adaptive immunity and escalating innate immunity within the CNS. Variables that cannot be controlled in the context of HIV-1 infections can be examined in nonhuman lentivirus systems, including control of age, antiretroviral therapies, viral strain, route and timing of infection, and accessibility to tissue samples that is not possible in humans. In addition, SIV and SHIV have been utilized in HIV-1 vaccine development (3, 44, 48, 69), and FIV has been used for therapeutic studies (9, 49). Lentiviral animal models also permit evaluation of viral evolution together with host pathogenic responses and thus represent invaluable tools to enhance the understanding of lentivirus neuropathogenesis.

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