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Leukocyte transmigration across the blood-brain barrier: perspectives on neuroAIDS

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1. ABSTRACT

Leukocyte trafficking serves a critical function in central nervous system (CNS) immune surveillance. However, in many disease states leukocyte entry into the CNS is increased, which can disrupt the blood-brain barrier (BBB) and propagate neuroinflammation. These pathologic processes result in BBB permeability, glial activation, and neuronal compromise, all of which contribute to CNS damage. The resulting neuronal injury and loss are characteristic of many neuroinflammatory conditions including Alzheimer disease, multiple sclerosis, HIV-1 encephalopathy, sepsis, ischemia and reperfusion, and CNS tumors. HIV-1 encephalopathy is unique among these processes in that viral activity exacerbates CNS immune dysregulation and promotes chronic neuroinflammation and neurodegeneration. Thus, a significant number of HIV-1-infected persons exhibit neurocognitive and/or motor impairment. This review discusses the mechanisms that regulate leukocyte recruitment into the CNS and how HIV-1 infection dysregulates this process and contributes to neuropathology. Experimental BBB models to study leukocyte transmigration and the potential of targeting this transmigration across the BBB as a therapeutic strategy are also discussed.

Table 1. Inflammatory mediators associated with HIV-1 CNS disease

HIV-1-Associated Inflammatory Mediator	CNS Activity
TNF-alpha (9, 13, 24, 429, 442, 471, 485, 635-638)	1) up-regulates cell adhesion molecules on cerebral microvascular endothelium and on astrocytes (139, 437-439, 639-641) 2) increases blood-brain barrier permeability (642) 3) induces CCL2 production by cerebral endothelial cells (540) 4) activates monocytes/macrophages (643) 5) enhances HIV-1 replication in microglia in presence of IL-1beta and IFN-gamma (26, 644) 6) induces oligodendrocyte apoptosis and myelin damage (644-647) 7) contributes to neuronal excitotoxicity by inhibiting astrocytic glutamate uptake (28) 8) induces reactive oxygen species-dependent neurotoxicity (648)
IL-1beta (9, 13, 471)	1) up-regulates cell adhesion molecules on cerebral microvascular endothelium (139, 438, 440, 639, 640) 2) induces CCL2 production by cerebral endothelial cells (540) 3) activates astrocytes (649, 650) 4) enhances HIV-1 replication in microglia in presence of TNF-alpha and IFN-gamma (26) 5) induces nitric oxide production by astrocytes (651)
IFN-gamma (13, 652)	1) induces nitric oxide production by microglia, macrophages, and astrocytes (651, 653, 654) 2) induces CCL2 production by cerebral endothelial cells (540) 3) enhances HIV-1 replication in microglia in presence of IL-1beta and TNF-alpha (26)
TGF-beta (485, 486, 655)	1) induces monocyte chemotaxis (656) 2) induces IL-1 expression by monocytes (656) 3) induces astrocyte chemotaxis (657) 4) inhibits glutamine synthetase activity in astrocytes which contributes to neuronal excitotoxicity (658)
CCL2/MCP-1 (429, 501, 552, 659)	1) induces monocyte, activated memory T-cell, and microglia chemotaxis (434, 506, 660) 2) enhances leukocyte viral replication, assembly, and release (25) 3) increased endothelial permeability through MMP activity and loss of tight junctions (341, 538, 539, 544) 4) disruption of adherens junctions (Roberts, T.K., manuscript in preparation)
CCL3/MIP-1alpha, CCL4/MIP-1beta (468, 507, 661)	1) induces monocyte and T-cell chemotaxis (662-664) 2) induces monocyte/macrophage activation (665)
CCL5/RANTES (468, 659)	1) induces monocyte and activated memory T-cell chemotaxis (666)
CXCL10/IP-10 (461, 528, 667-669)	1) induces activated T-cell chemotaxis (668, 670) 2) enhances HIV-1 replication in monocytes/macrophages and lymphocytes (671) 3) induces caspase-3-mediated neuronal apoptosis (528, 667)
CX3CL1/Fractalkine (672-675)	1) induces microglia activation and chemotaxis (676) 2) induces monocyte chemotaxis (674)
SDF (cleaved form) (29, 677)	1) direct neurotoxicity (29, 677)
Leukotrienes (9, 24)	1) increases blood-brain barrier permeability (678)

2. INTRODUCTION

Leukocyte transmigration across the BBB is a complex, well coordinated process. In non-pathological states, leukocytes conduct homeostatic CNS immune surveillance (1, 2). However in HIV-1 infection, monocyte diapedesis is an important mechanism for viral entry into the CNS (3). In fact, HIV-1 has been detected in the brain as early as fifteen days post-peripheral blood exposure (4). Once in the CNS, monocytes differentiate into perivascular macrophages and are also thought to replenish aging microglia populations (1, 2, 5-8). Infected CNS monocytes/macrophages and microglia release infectious virus, as well as viral proteins and inflammatory mediators, that activate parenchymal cells and are toxic to neurons (Table 1) (9, 10). Resident macrophages and microglia both become infected with HIV-1 and are able to support robust viral replication and assembly (3, 11-18). In contrast, astrocytes become infected at low levels and are able to synthesize viral products, but are believed to be unable to support substantial infectious virion production (12, 19-23). Collectively, resident immune cells and glia serve as CNS viral reservoirs (3). The virus, viral proteins, cytokines, and chemokines produced by infected cells activate additional resident macrophages, microglia, and astrocytes and cause these cells to become more permissive to viral replication, to release neurotoxic factors, to compound the release of inflammatory mediators, and to recruit additional leukocytes into the CNS (9, 24-27).

Although not directly infected by HIV-1 (12), neurons are particularly sensitive to inflammation and are affected by viral proteins and inflammatory mediators (Table 2). Viral proteins and cellular factors released from activated glia and phagocytes are directly neurotoxic, while astrocyte activation and/or infection results in cellular dysfunction and the inability to regulate the CNS metabolic environment (28-31). Both viral proteins and inflammatory mediators promote BBB dysfunction including loss of barrier integrity and endothelial cell hypertrophy, and possibly apoptosis (Table 3) (32, 33). Blood-brain barrier dysfunction contributes to increased leukocyte transmigration, free virus entry, and loss of metabolic homeostasis in the CNS. Viral, inflammatory, and metabolic insults result in neuron dysfunction, myelin damage, and neuronal apoptosis (33-38). The ensuing neuroinflammation and metabolic encephalopathy promote a self-perpetuating cycle of leukocyte recruitment into the CNS, macrophage and glial activation, glial proliferation, and neuronal damage and death.

CNS immune activity continues throughout infection, resulting in the accumulation of HIV-1-mediated neurodegeneration over an individual's lifetime. Despite antiretroviral therapy (ART), neuroinflammation and low

Table 2. Neurotoxic and inflammatory compounds that contribute to HIV-1 encephalopathy

Host Factors	Viral Factors
mediators of neuronal oxidative damage: nitric oxide (679-681) superoxide (448, 682, 683) peroxynitrite (448, 684) hydroxyl radicals (685) hydrogen peroxide (686)	**tat**: Ca^{2+} flux through N-methyl-D-aspartate (NMDA) receptor leading to nitric oxide-mediated neuronal apoptosis (559, 687-692) non-NMDA glutamate receptor activation (693) cytokine and chemokine induction and resultant neurotoxicity (693)
mediators of neuronal excitotoxicity: glutamate (694-696) quinolinic acid (636, 697-700) platelet activating factor (24, 701-703) arachidonic acid metabolites (9, 24, 704)	**gp120**: reduced glutamate uptake and metabolism by astrocytes leading to glutamate-mediated excitotoxic neuronal apoptosis (30, 31, 541, 705, 706) direct interaction with neurons leading to impaired glycolytic metabolism and cell survival (707)
excessive inflammatory chemokines: (promote cellular activation and chemotaxis) CCL2/MCP-1 (429, 501, 507, 552, 659) CCL3/MIP-1alpha (468, 507) CCL4/MIP-1beta (468, 507, 661) CCL5/RANTES (468, 659) CXCL10/IP-10 (461, 528, 668, 669) CXCL12/SDF-1alpha (708-710) CX3CL1/fractalkine (672, 673, 675)	**gp41**: excessive NO and glutamate release and reduced glutamate uptake by astrocytes promoting neuronal apoptosis (679, 711-713) reduced neuronal glutathione and disruption of mitochondrial function leading to neuronal apoptosis (714)
excessive inflammatory cytokines: (promote cellular activation and dysfunction) TNF-alpha (9, 13, 24, 429, 442, 471, 485, 635) IL-1beta (9, 13, 471) IFN-gamma (13, 652)	**nef**: neurotoxic and glialtoxic through inhibition of K^+ channels (530, 715-718) and through induction of IP-10 (528)
soluble peptides: sPECAM-1 (446), sICAM-1 (719-722), sVCAM-1 (721-723), sCD40L (724, 725), sIL-2R (652, 726, 727), sCD14 (728-731), MMPs (459, 460, 536), substance P (732, 733) (associated with inflammation, cellular activation, and blood-brain barrier disruption) sFasL (734, 735) (produced upon leukocyte activation and/or HIV-1 infection and associated with astrocytic apoptosis)	**vpr**: neuronal and astrocytic apoptosis through insertion into cell membranes and formation of cation-selective channels that promote Na^+ entry into cells (736-741) **rev**: neurotoxic through interaction with acidic phospholipids and disruption of membrane integrity (742)

Table 3. Mediators of blood-brain barrier dysfunction in HIV-1 infection

Mediator	Effect on Blood-Brain Barrier
TNF-alpha	increased blood-brain barrier permeability through MMP-mediated disruption of tight junctions (403, 743)
CCL2	increased blood-brain barrier permeability through MMP activity, loss of tight junctions, and formation of stress fibers (341, 538, 539, 543)
Tat	increased blood-brain barrier permeability through induction of focal adhesion kinase, CCL2, NO, and MMPs (480, 481, 509, 511)
gp120	increased blood-brain barrier permeability through induction of TNF-alpha and NO, loss of tight junction proteins, endothelial cytoskeletal reorganization, and direct cytotoxicity to endothelial cells (523-526)
Nef	increased blood-brain barrier permeability through MMP-9 activity (536)
NO and Peroxynitrite	increased blood-brain barrier permeability through phosphorylation of tight junction proteins (454, 681)
Matrix Metalloproteinases (MMP)	increased blood-brain barrier permeability through proteolytic degradation of cell adhesion molecules and extracellular matrix proteins (536, 744, 745)

level CNS viral infection persist, resulting in cognitive impairment in 40-50% or more of HIV-1-infected individuals (39-42). ART significantly prolongs the life of many infected individuals; therefore, neurocognitive and motor dysfunction have become major health concerns for individuals living with chronic HIV-1 disease. Neurological dysfunction may be further compounded by age (43-46), diabetes (47), hepatitis C viral infection (48-50), other neurodegenerative conditions such as Alzheimer disease (51-54), and by substance abuse (55-57).

Monocytes, and to a lesser extent CD4+ T cells, are the predominant vehicle by which HIV-1 enters the brain (58). Release of inflammatory mediators by glia and CNS phagocytes in response to viral infection, viral protein, or cellular activation initiates an inflammatory cascade that results in aberrant leukocyte transmigration into the CNS, BBB disruption, metabolic derangement of the extracellular CNS environment, glial dysfunction, and neuronal injury and loss. In fact, the number of recruited monocytes and degree of monocyte/macrophage/microglia activation is a better prognostic indicator of neurocognitive decline and marker of CNS pathology than is peripheral or CSF (cerebrospinal fluid) viral load (11, 13, 59-61). As HIV-1-infected leukocyte entry into the CNS is an initiating event in HIV-1-mediated neuropathology, a significant focus of this review is on the mechanisms of leukocyte transmigration across the BBB and how HIV-1, its proteins, and excessive cytokines and chemokines dysregulate this process. Models for studying leukocyte transmigration and the potential targeting of leukocytes as a means of therapy are also discussed.

3. THE BLOOD-BRAIN BARRIER AND LEUKOCYTE TRANSMIGRATION

3.1. The blood-brain barrier and interendothelial junction

Neuroinflammation that results from transmigration of HIV-1-infected and activated leukocytes

Table 4. Adhesion molecules involved in leukocyte transmigration into the CNS

Endothelial Cell Adhesion Molecule	Predominant Leukocyte Binding Partner	Step in Transmigration
E-Selectin (CD62E) P-Selectin (CD62P)	PSGL-1 (CD162)	Rolling and Tethering (132, 134, 136, 746)
GlyCAM-1 (CD34) PSGL-1 (CD162)	L-Selectin (CD62L)	Rolling and Tethering (746-748)
VCAM-1 (CD106)	VLA-4/alpha$_4$-beta$_1$ (CD49d/CD29)	Rolling, Tethering, and Arrest (142-145)
ICAM-1 (CD54)	LFA-1/alpha$_L$-beta$_2$ (CD11a/CD18) Mac-1/alpha$_M$-beta$_2$ (CD11b/CD18)	Arrest, Locomotion, and Diapedesis (173, 174, 201, 749)
ICAM-2 (CD102)	LFA-1 (CD11a/CD18) Mac-1/alpha$_M$-beta$_2$ (CD11b/CD18)	Arrest, Locomotion, and Diapedesis (173, 174, 201, 750)
JAM-A (CD321)	LFA-1/alpha$_L$-beta$_2$ (CD11a-CD18)	Locomotion and Diapedesis (213, 226, 230-232)
JAM-B (CD322)	VLA-4/alpha$_4$-beta$_1$ (CD49d/CD29) JAM-C (CD323)	Locomotion and Diapedesis (238)
JAM-C (CD323)	Mac-1/alpha$_M$-beta$_2$ (CD11b/CD18)	Locomotion and Diapedesis (241, 248)
PECAM-1 (CD31)	PECAM-1 (CD31)	Locomotion, Diapedesis, Migration through Basement Membrane (251-255, 258)
CD99	CD99	Diapedesis (200, 269, 270, 272)
PVR (CD155)	DNAM-1 (CD226)	Diapedesis (278)
PrP^C (CD230)	PrP^C (CD230)	Diapedesis (288)

is the predominant pathologic process in neuroAIDS. To enter the CNS, leukocytes must cross the specialized microvasculature of the BBB. Non-fenestrated endothelial cells and their basement membrane form the major anatomical unit of the BBB (62) and are the initial barrier to influx of molecules and cells into the CNS (63). Interactions between endothelial integrins and dystroglycans with matrix proteins anchor the endothelium and contribute to barrier properties (64-68). Astrocytes extend their end-feet from the parenchyma toward the abluminal vascular face to abut endothelial cells. The basement membrane elaborated by astrocytes forms the glial limitans perivascularis and is an important second barrier to leukocyte ingress (63, 69-72). In CNS capillaries, these two membranes are fused. However in post-capillary venules, there is a perivascular space between the endothelial basement membrane and the glial limitans. Macrophages and microglia reside within this space and further regulate the entry of molecules and cells into the CNS by phagocytosis and the elaboration of soluble factors (69, 70, 73). Pericytes, which have both smooth muscle-like and phagocytic properties, are within the endothelial basement membrane and also influence the endothelium and its perivascular environment (74-78). Neurons directly innervate astrocytes and endothelial cells and provide additional control over BBB properties (79-84). Endothelial cells, pericytes, macrophages, astrocytes, and neurons all contribute to the unique phenotype of CNS vessels by releasing factors in a regulated manner that collectively control the dynamic properties of the BBB (71, 72, 76-95). These factors include: enzymes, cytokines, chemokines, glial and endothelial trophic factors, and neurotransmitters.

The BBB is both an anatomical and physiological barrier. Endothelial cells express intercellular adhesion proteins that form complexes in the interendothelial space (96-98). They also express efflux transporters that actively transport molecules out of endothelial cells (99-106), and membrane transporters and receptors that permit passage of only select molecules into endothelial cells (107-113). These transporters regulate the transcellular entry of ions and molecules into the CNS. Brain microvascular endothelial cells (BMVEC) have low pinocytic activity, which further diminishes cellular uptake of substances (97). Collectively, these properties restrict the paracellular (between endothelial cells) and transcellular (through endothelial cells) movement of ions, molecules, microparticles such as viruses, and cells into the CNS.

The interendothelial adhesion proteins that maintain BBB integrity can generally be categorized as those that act homotypically and/or heterotypically between endothelial cells, those that form tight junctions, and those that establish adherens junction complexes. To cross the interendothelial space, a leukocyte must disrupt all of these interactions while still maintaining barrier properties. Then it must traverse the dense matrix of the basement membrane to conduct immune surveillance in the perivascular space. During injury or inflammation, leukocytes must additionally cross the glial limitans to enter the neuropil (6, 114-116). Transmigration is an exquisitely controlled process, and leukocytes are able to transmigrate constitutively across the BBB with selectivity and efficiency without barrier disruption. The major mechanisms that regulate leukocyte transmigration include: (1) chemokine and cytokine-induced affinity maturation and increased expression of intercellular adhesion proteins on both endothelial and leukocyte cell surfaces and (2) intracellular signaling-mediated tight junction and adherens junction disassembly and cytoskeletal rearrangement.

3.2. Multi-step model of transmigration

The recruitment of leukocytes into the CNS is a complex process that requires interaction between proteins expressed on the leukocyte and the vasculature (Table 4). The chemokine- and cytokine-regulated activation state of both the leukocyte and endothelium influences the ability of leukocytes to negotiate the BBB. Sequential expression of specific adhesion molecules, their affinity and avidity for binding ligands, and intracellular signaling that alter these interactions and the morphology of the leukocyte and endothelial cell all regulate transmigration. A multi-step model of leukocyte diapedesis across endothelial barriers includes: leukocyte tethering and rolling, activation and arrest, locomotion, diapedesis, and traverse across the basement membrane. Although specific stages have been defined, these events do not act independently and the coordination of these events is still not clear. Intracellular

signaling initiated by early events influences later steps in transmigration.

3.2.1. Tethering and rolling

Leukocytes tumble and roll along endothelial margins as they travel through the blood. This loose association is mediated by low- and high-affinity binding between selectins and their glycosylated ligands, which all contain the sialyl-Lewis^X carbohydrate motif (117-119). P-selectin is stored in Weibel-Palade bodies of endothelial cells and can be rapidly mobilized to the apical surface upon cell activation (120, 121). Its primary ligand is P-selectin glycoprotein ligand-1 (PSGL-1) (122, 123), a surface glycoprotein on leukocytes, particularly myeloid cells (122, 124). E-selectin is apically expressed on cytokine-activated endothelium and recognizes many sialyl-Lewis^X containing glycoproteins, including PSGL-1 (119, 123, 125, 126). L-selectin is constitutively expressed on all leukocytes and its surface expression is regulated by metalloproteinase cleavage of the extracellular domain (127-129). L-selectin binds PSGL-1 on inflamed endothelium (124). Selectin-ligand interactions are characterized by long binding distances to initiate capture (130), high on/off rates to facilitate rolling (131), and sufficient mechanical strength to withstand shear stress (132). Cytokine and chemokine activation of leukocytes and endothelial cells up-regulates selectins and their ligands, increasing the ability of leukocytes to be tethered to the vasculature. In addition, selectin binding propagates intracellular signals that activate transcriptional regulators. In monocytes, for example, NF-kappa B activity promotes the synthesis and release of TNF-alpha and CCL1 which up-regulate adhesion molecules on the leukocyte and endothelium and enhance the affinity of these proteins for their ligands (133). Thus, engagement of selectins with their ligands on activated endothelium initiates events that increase the ability of endothelial cells to bind leukocytes.

Interactions between P-selectin on endothelial cells and leukocyte PSGL-1 are an initiating event in capturing leukocytes from the blood (122, 134). Oligomerization of P-selectin and PSGL-1 enhances this binding (135). E-selectin binding interactions stabilize leukocyte rolling and allow it to slow its tumbling over the vasculature (136). For leukocytes to adhere firmly to the endothelial surface while traveling at high flow rates, additional adhesion molecules must be expressed and activated on the leukocyte and endothelium. This is accomplished by both outward-in and inward-out signaling. Outward-in signaling is the response of leukocytes and endothelial cells to ligation of adhesion molecules by their cognate ligand. These binding events promote cytokine and chemokine expression, mobilization and *de novo* synthesis of additional adhesion molecules, and conformational changes in surface adhesion molecules that enhance their binding ability. The effect of cytokines and chemokines on the expression and activity of cell adhesion molecules is also important. Endothelial cells present chemokines to leukocytes by binding them to membrane-bound glycosaminoglycans on the extracellular surface (137) or by expressing chemokines that are transmembrane proteins (138). As the leukocyte is slowed by the tethering of selectins to PSGL-1, its chemokine receptors interact more efficiently with chemokines. Chemokine receptors are G-protein coupled and transduce intracellular signals. This inward-out signaling modulates the activation status of the leukocyte, induces leukocyte cytokine and chemokine expression, alters the cytoskeletal framework of the leukocyte, and facilitates cellular spreading and uropod formation. It can also promote the expression of additional surface adhesion molecules and alter their affinity for ligands. Thus, affinity (strength of a single bond) and avidity (total strength of all bonds between two cell adhesion molecules) alterations in cell adhesion molecules can be induced by their direct ligation (outward-in signaling) and by chemokine-induced activation (inward-out signaling).

Vascular cell adhesion molecule-1 (VCAM-1), a member of the immunoglobulin gene superfamily, is an important endothelial adhesion molecule that is apically expressed in response to cytokine activation (139, 140). The tethering and rolling of leukocytes over activated endothelium allows the leukocyte to be further slowed by interactions between VCAM-1 and its leukocyte ligand, very late antigen-4 (VLA-4) (141, 142). The VCAM-1/VLA-4 interaction promotes leukocyte arrest on the vasculature and can also occur without significant selectin tethering (143, 144). Leukocyte slowing over endothelium facilitates chemokine interaction with receptors on the leukocyte. Through inward-out signaling, chemokines increase the affinity of VLA-4 for VCAM-1 (145, 146). Affinity maturation involves unfolding of the extracellular domain of the integrin such that the globular head, with its ligand binding site, is extended beyond the membrane surface (147). Thus, VLA-4/VCAM-1 interactions promote a transition from leukocyte tethering and rolling to firm adherence to the endothelium.

Stable binding of VLA-4 to VCAM-1 results in outward-in signaling within the leukocyte that promotes cytoskeletal rearrangements and subsequent changes in leukocyte morphology. Paxillin is recruited to the cytoplasmic tail of VLA-4's alpha chain upon ligation by VCAM-1 (148). VLA-4/paxillin interactions destabilize lamellipodia and restrict lamellipodia formation to the anterior edge of the leukocyte (149, 150). This promotes directional leukocyte migration and contributes to leukocyte movement towards interendothelial junctions (149, 150). Disruption of VLA-4/paxillin binding reduces leukocyte recruitment to sites of inflammation *in vivo* (151). VLA-4/VCAM-1 interactions are not only important for adherence of leukocytes to inflamed endothelium, but also for the directional migration of leukocytes that facilitates diapedesis.

VLA-4 ligation of VCAM-1 also induces outward-in signaling in the endothelial cell. VCAM-1 engagement activates Rac1, a small GTPase that can induce reactive oxygen species and phosphorylation of p38 MAPK (mitogen-activated protein kinase) (152). Reactive oxygen species activate the kinase Pyk2, which promotes phosphorylation of beta-catenin and dissociation of beta-catenin from adherens junction complexes (153). This

destabilizes the adherens junction, promotes gap formation between endothelial cells, and increases endothelial permeability (154). Activity of the oxidant-sensitive kinase p38 promotes actin stress fiber formation (155) and is associated with loss of adherens junction complexes and increases in endothelial permeability (156). Together, the VCAM-1-mediated activity of reactive oxygen species and p38 alter the integrity of endothelial barriers and promote leukocyte diapedesis (152, 154, 157, 158). Thus, the signaling events initiated in leukocytes and endothelial cells by VLA-4/VCAM-1 interactions functionally and morphologically alter the leukocyte and endothelium and promote successive stages in transmigration.

3.2.2. Activation and arrest

Although VLA-4/VCAM-1 interactions initiate leukocyte arrest, additional interactions are required to maintain leukocyte adherence to endothelial cells under shear stress. Intercellular adhesion molecule-1 and -2 (ICAM-1 and ICAM-2), which bind the $beta_2$ integrin leukocyte function antigen-1 (LFA-1), contribute to this stage of transmigration (159-161). ICAM-1 and ICAM-2 are constitutively expressed on endothelial cells, with ICAM-1 being up-regulated by inflammatory cytokines (162). They both have high affinity for leukocyte LFA-1, which can be induced into high-affinity states by both outward-in and inward-out signaling. Early during tethering, E-selectin engagement induces an LFA-1 conformation of intermediate affinity for ICAM-1 (163). This enhances tethering and promotes adherence of leukocytes to the endothelium (164). Subsequent chemokine activation of leukocytes induces affinity maturation of LFA-1 into high binding states and causes lateral integrin clustering, both of which increase the binding avidity of LFA-1 for ICAM-1 (165-168). Binding of ICAM-1 to LFA-1 also induces outward-in signaling and LFA-1 affinity modulation (169, 170). Conversion of LFA-1 to a high affinity state involves interposition of the actin-binding protein talin-1 between the alpha and beta chains of LFA-1 (170-172). This stabilizes the extracellular spatial configuration of LFA-1 and creates a stronger binding interface for ICAM-1. The effect of LFA-1/ICAM-1 interactions is sustained adhesion between leukocytes and endothelial cells under flow conditions.

ICAM-2 also binds LFA-1 and contributes to leukocyte adherence and transmigration (173, 174). Because expression of ICAM-2 is not inducible, it is likely that it maintains leukocyte endothelial arrest, allowing the interaction of leukocytes with endothelial cells to increase cytokine- and chemokine-induced up-regulation of ICAM-1 and affinity maturation of LFA-1. ICAM-1 and ICAM-2 also bind Mac-1 (175-177), another $beta_2$ integrin with similar activity and overlapping, but different leukocyte subset specificity than LFA-1. LFA-1 is expressed on virtually all lymphocytes (178, 179), while Mac-1 is expressed on only a small subset of T-cells (180). Mac-1 is expressed on monocytes/macrophages and eosinophils (179-181), while LFA-1 is not expressed on eosinophils and has less expression on monocytes/macrophages when compared to Mac-1 (179). The specific expression and relative abundance of integrins on leukocyte populations likely regulates the recruitment of the appropriate leukocyte to a particular vascular bed.

Binding of VLA-4 to VCAM-1 and LFA-1 to ICAM-1 induces clustering of these adhesion molecules in the leukocyte and endothelial membrane. As a result, a ring-like structure of cell adhesion molecules forms at the interface between the leukocyte and endothelial cell (182, 183). This structure on endothelial cells has been termed the transmigratory cup and is believed to be a docking structure for leukocytes (184, 185). Depending on the quantity and type of adhesion molecules present and their spatial distribution, specific leukocytes can then be guided in the transmigratory cup to either the interendothelial junction for paracellular transmigration or can be induced to pass transcellularly through the endothelial cell in involuting channels (discussed below) (185, 186). The specific proteins and activating conditions that direct leukocytes to migrate paracellularly or transcellularly are not well defined.

LFA-1/ICAM-1 interactions induce Src-mediated tyrosine phosphorylation of the actin binding protein cortactin (187-190). This links ICAM-1 to the endothelial cytoskeleton which maintains clustering of ICAM-1 molecules and enables cytoskeletal remodeling around the transmigrating leukocyte (189, 190). VCAM-1 also becomes concentrated in this ring-like structure (184). Interactions with the actin-binding proteins ezrin, moesin, alpha-actinin, and vinculin anchor VCAM-1 to the cytoskeleton and maintain the docking structure during endothelial cell morphology changes (184). Transmigratory cup formation and leukocyte diapedesis can be impeded by inhibition of Rho GTPase, a downstream mediator of ICAM-1 signaling (183, 191). Inflammatory stimulation of BMVEC further strengthens interactions between the leukocyte and transmigratory cup. Specifically, TNF-alpha and IFN-gamma promote increased endothelial expression and transmigratory cup localization of ALCAM (activated leukocyte cell adhesion molecule) (192), a member of the immunoglobulin gene superfamily (193, 194). Through binding to CD6 on leukocytes (194), ALCAM promotes leukocyte transmigration. Antibody blocking of either endothelial ALCAM or leukocyte CD6 results in significant reductions in leukocyte transmigration (192, 195). In particular, monocytes, CD4 T-cells, and B-cells are restricted from crossing the BBB, whereas CD8 T-cell transmigration is unaffected (192).

3.2.3. Locomotion

Leukocytes follow a haptotactic gradient of chemokines and adhesion molecules expressed on the surface of the endothelium to direct them to paracellular compartments (196-198), particularly tricellular corners (199, 200). This phase is termed locomotion (201). Five members of the immunoglobulin gene superfamily expressed on endothelial cells, ICAM-1, ICAM-2, JAM-A (junctional adhesion molecule-1), JAM-C, and PECAM-1 (platelet endothelial cell adhesion molecule-1), are important to this process. ICAM-1, ICAM-2, and JAM-A bind leukocyte LFA-1 (159-161); while ICAM-1, ICAM-2, and JAM-C interact with leukocyte Mac-1 (175-177).

These are heterotypic protein interactions in that binding occurs between different proteins. Endothelial PECAM-1 binds identical PECAM-1 on the leukocyte in a homotypic manner. ICAM-1, ICAM-2, JAM-A, JAM-C, and PECAM-1 are highly expressed in regions where multiple endothelial cells are interposed. This arrangement is vital to directing leukocytes to points of easiest penetration. In studies where ICAM-1 and ICAM-2 are blocked from binding leukocyte LFA-1 and Mac-1, monocytes are found to pirouette on their uropod and are unable to home to interendothelial junctions (201). In mouse models deficient in Mac-1, leukocytes have inefficient homing to the paracellular junction (202).

3.3. Paracellular diapedesis

Once properly directed to the paracellular compartment, the leukocyte extends its pseudopod into the intercellular junction and moves between endothelial cells in an amoeboid-like fashion. However to reach the perivascular space, the leukocyte must penetrate the junctional complexes that maintain the integrity of the BBB. Leukocytes are able to disrupt these interactions transiently in a manner that maintains barrier properties. This is accomplished, in part, through competitive binding of adhesion molecules on the leukocyte with those on the endothelium. At the leading edge of leukocyte transmigration, adhesion complexes between apposed endothelial cells protrude into the paracellular compartment. Molecular partners expressed on the leukocyte compete for these binding interactions and form homotypic and heterotypic bonds with the endothelium. In a "zipper-like" manner, leukocytes are chaperoned through the interendothelial space without compromising barrier integrity.

Diapedesis through the endothelial paracellular space is complex. The phenotype of both the leukocyte and the vascular bed regulate leukocyte transmigration. Thus, descriptions of leukocyte diapedesis can at best generalize the process. Many proteins contribute to diapedesis including LFA-1, Mac-1, JAM-A, JAM-B, JAM-C, PECAM-1, CD99, PVR, DNAM-1, and PrP^C. These adhesion molecules are differentially expressed on leukocyte subsets and under specific inflammatory conditions. For example, PECAM-1 is on monocytes and neutrophils, but is found on only a small subset of T-cells (197, 203, 204). CD99 is expressed at low density on neutrophils (200), while PrP^C is ubiquitously expressed on monocytes and lymphocytes but is absent on mature granulocytes (205). IL-1beta is associated with PECAM-1-dependent leukocyte diapedesis (206, 207), while TNF-alpha and IFN-gamma reduce PECAM-1 expression, junctional localization, and contribution to transmigration (208-210).

3.3.1. JAM-A

JAM-A is a surface protein found on both leukocytes (211, 212) and endothelial cells (211-214) that participates in leukocyte transmigration and maintenance of barrier properties. The CNS vasculature expresses high levels of this adhesion molecule (215, 216). JAM-A localizes to the apical aspect of endothelial intercellular junctions (211-214, 216) in association with tight junction complexes (213, 214, 216) and therefore contributes to junctional stability and impermeability (214, 217). It forms homotypic interactions with JAM-A molecules on apposing endothelial cells (218). Specifically, JAM-A forms inverted U-shaped homodimers *in cis* that then bind *in trans* to similar homodimers on adjacent endothelial cells (219). The cytoplasmic tail of JAM-A contains a PDZ-binding domain (PSD-95/disc large/zonula occludens protein-1) that enables JAM-A to bind to the cytoplasmic proteins ZO-1 (zonula occludens-1) (220-222), AF-6 (ALL-1 gene fusion partner-6; afadin) (222), and PAR-3 (proteinase-activated receptor-3) (221, 223). ZO-1 acts as a scaffold that links JAM-A to the tight junction integral protein occludin (220) and to filamentous actin (224). AF-6 also associates with ZO-1 and interacts with the actin cytoskeleton through association with profilin (225). PAR-3 acts as a nucleating factor that links JAM-A to the cell polarity-regulating proteins PAR-6, atypical PKC (protein kinase C), and Cdc42 (223). The cytoplasmic tail of JAM-A also interacts with cingulin, which strengthens the interaction of JAM-A with the cytoskeleton (220). Thus, JAM-A can affect cell polarity, cytoskeletal remodeling, and tight junction- and cadherin-based adhesive properties. These interactions enable JAM-A to regulate the interendothelial space.

Under inflammatory conditions, particularly TNF-alpha and IFN-gamma stimulation, JAM-A is redistributed to the luminal surface where it participates in leukocyte homing to the paracellular space (226, 227). LFA-1 on leukocytes binds to endothelial JAM-A, facilitating the entry of leukocytes into the paracellular compartment (226, 228). Endothelial JAM-A partitions to the ring-like structure that surrounds the pseudopod of penetrating leukocytes at the junctional interface (182). As the leukocyte enters the paracellular space, LFA-1 disrupts homophilic JAM-A/JAM-A interactions (229). The bond between LFA-1 and JAM-A can withstand pulling forces better than JAM-A homophilic interactions (229). This allows the leukocyte to progress through the intercellular space. Antibody blocking of JAM-A disrupts leukocyte endothelial arrest and transmigration both *in vitro* and *in vivo* (213, 230, 231). Studies with JAM-A deficient endothelial cells support these findings and demonstrate accumulation of leukocytes above the paracellular compartment (232). Once through the apical aspect of the interendothelial junction, JAM-A/JAM-A interactions reform and reseal the endothelial barrier. Thus, JAM-A acts as a bidirectional zipper that can open the endothelial barrier in front of the transmigrating leukocyte and reform junctional complexes at the trailing edge of the leukocyte to reestablish the barrier.

3.3.2. JAM-B and JAM-C

JAM-B and JAM-C are also concentrated at apical endothelial intercellular junctions (216, 233, 234). JAM-B forms heterotypic bonds with both leukocyte JAM-C (235, 236) and VLA-4 (237). JAM-B/VLA-4 interactions require prior priming by binding of JAM-B with leukocyte JAM-C (237). JAM-B promotes leukocyte transmigration, as blocking JAM-B with antibody or soluble JAM-B

disrupts diapedesis (238). Endothelial JAM-B also forms heterotypic bonds with endothelial JAM-C (239), and endothelial JAM-C binds homotypically with JAM-C on apposed cells (239). These interactions contribute to endothelial barrier properties. JAM-B/JAM-C and JAM-C/JAM-C interactions promote signaling through the PDZ domain-binding motif of JAM-C which influences stability of VE-cadherin (vascular endothelial cadherin; cadherin-5) complexes (240). Up-regulation of JAM-C on inflamed endothelium facilitates lateral spreading of VE-cadherin away from the adherens junction. This promotes transient adherens junction disassembly and causes directional motion of leukocytes toward the abluminal face of the vasculature. Experimentally-induced over-expression of JAM-C in endothelial cells causes increased barrier permeability and enhanced leukocyte transmigration (241, 242), while loss of JAM-C results in accumulation of leukocytes in the peripheral blood rather than in inflamed tissue (243). Antibody blocking of JAM-C interactions with JAM-B or JAM-C reduces leukocyte transmigration and recruitment to inflammatory sites (242, 244, 245). This has been attributed to increased reverse transmigration of the leukocyte (245). The implication is that engagement of JAM-C by homotypic and/or heterotypic interactions with apposing endothelial cells or transmigrating leukocytes promotes opening of the adherens junction through signaling to VE-cadherin. This promotes unidirectional movement of the leukocyte through the paracellular space. JAM-C also binds leukocyte Mac-1 (246, 247) which enables it to recruit leukocytes into the paracellular compartment and guide them through the initial stages of transmigration. Antibody to or soluble forms of JAM-C inhibit leukocyte extravasation both *in vitro* and *in vivo* (241, 248). Simultaneous blocking of JAM-C and PECAM-1 almost completely abolishes leukocyte transmigration (248), while a greater percentage of leukocytes accumulate at the luminal vascular surface when JAM-A is blocked than when PECAM-1 is blocked (231). This suggests that JAMs function at a stage of transmigration slightly upstream of PECAM-1.

3.3.3. PECAM-1

PECAM-1 is enriched at endothelial junctions (249, 250) and contributes to transmigration of monocytes, neutrophils, natural killer cells, and certain T-cell populations (197, 206, 251-257). In studies using PECAM-1-specific antibodies and peptides, leukocyte transmigration is blocked by 70-90%, regardless of whether endothelial cells or leukocytes are pre-treated with the blocking compound (251). *In vivo* blocking antibody studies demonstrate reduced neutrophil recruitment into inflamed tissue (252, 253, 258). Neutrophil recruitment to inflammatory sites is also significantly reduced in PECAM-1 knockout mice (254). The extracellular structure of PECAM-1 contains six immunoglobulin-like domains. Antibody blocking of the first two domains prevents monocyte diapedesis at an early step such that monocytes accumulate on the apical aspect of the endothelium (253, 255, 258). Blocking the sixth domain causes monocytes to accumulate in the interendothelial space and between endothelial cells and the basement membrane (206, 255). Domains 1 and 2 of PECAM-1 are sites of homotypic binding, while domain 6 interacts heterotypically with heparin sulfate in the extracellular matrix (259-261). Thus, PECAM-1 participates in multiple steps of leukocyte transmigration by engaging different adhesion molecules at distinct binding sites, and plays a central role in leukocyte transmigration, contributing to homing, diapedesis, and migration through the basal lamina.

PECAM-1 ligation activates leukocyte integrins. Antibody-mediated activation of leukocyte PECAM-1 enhances the ability of leukocytes to adhere to VCAM-1 through VLA-4 interactions and to fibronectin through VLA-4 and VLA-5 (203). Similarly, cross linking leukocyte PECAM-1 with antibody increases LFA-1-mediated binding to ICAM-1 (203, 256). When neutrophil PECAM-1 interacts with endothelial PECAM-1, the integrin $alpha_6beta_1$ (VLA-6) is up-regulated on the surface of the transmigrating neutrophil (262). Because the extracellular matrix protein laminin is the major ligand of VLA-6 (263), antibody blocking of VLA-6 or genetic knockdown of PECAM-1 results in an inability of neutrophils to migrate through the basement membrane and accumulate in sites of inflammation (262). This suggests that leukocyte PECAM-1 engagement of endothelial PECAM-1 results in intracellular signaling that increases the avidity of integrins for their ligands, enhancing leukocyte adhesion (203, 256, 264, 265) and transmigration (256, 262). It has not been established how PECAM-1 signaling mediates these events. Thus, PECAM-1's binding interactions guide leukocytes through the interendothelial space and basal lamina. Additionally, PECAM-1 acts as an activation signal, altering the phenotype of the leukocyte to enhance its ability to enter the interendothelial space and negotiate the basement membrane.

As the leukocyte interacts with endothelial PECAM-1 at the apical face and in the paracellular space, PECAM-1 is rapidly recycled from a reticulum of 50 nm vesicles beneath the endothelial surface to the leading edge of leukocyte transmigration (266). This subsurface membrane reticulum, referred to as the lateral border recycling compartment (LBRC), is contiguous with the lateral endothelial cell border and constitutively traffics to the surface with a half-life of approximately ten minutes (266). Nearly one-third of total cellular PECAM-1 exists in the LBRC (266). Thus, PECAM-1 can be rapidly mobilized to the cell surface and targeted to the site of leukocyte diapedesis (266, 267). This allows PECAM-1-rich membrane to surround the leukocyte and create a haptotactic gradient to guide transmigration between apposed endothelial cells. If homotypic PECAM-1 interactions between the leukocyte and endothelial cell are inhibited at the apical surface, both targeted recycling of PECAM-1 from the LBRC to the lateral cell surface and leukocyte transmigration are blocked (266). Src kinase mediates this signaling, as inhibition of Src activity specifically disrupts LBRC targeting and leukocyte transmigration (268). If kinesin motors are inhibited or microtubules are depolymerized, targeted LBRC recycling and leukocyte diapedesis, but not constitutive LBRC trafficking, is blocked (267). Thus, upon PECAM-1 ligation, Src-dependent intracellular signaling induces

kinesins to redirect PECAM-1-rich membrane of the LBRC toward the lateral endothelial face to the site of leukocyte diapedesis. As a result, space is created between apposed endothelial cells to accommodate the transmigrating leukocyte. In addition, unligated PECAM-1 becomes available for homotypic interaction which may propagate continuous targeting of the LBRC to the leading edge of leukocyte transmigration.

3.3.4. CD99

CD99 is enriched at endothelial cell lateral borders and is involved in leukocyte transmigration through the paracellular compartment (269, 270). CD99 is structurally distinct from all other identified cell adhesion molecules (271). It also binds in a homotypic manner and helps to maintain barrier properties while simultaneously acting as a regulator of leukocyte transmigration (200, 269, 270, 272). CD99 does not appear to participate in leukocyte arrest, as antibodies against CD99 do not interfere with leukocyte adhesion to endothelium (200, 269, 270). However, CD99 does participate in leukocyte diapedesis. Antibodies to CD99 block 80-90% of leukocyte transmigration (200, 269), and blocking both PECAM-1 and CD99 almost completely abolishes leukocyte transmigration (200, 269). Antibody to CD99 causes leukocytes to accumulate specifically near tricellular corners within the paracellular space at a point distal to where they accumulate when PECAM-1 is blocked (200, 269). Thus, CD99 appears to function at a step successive to PECAM-1 in diapedesis. In neutrophils, CD99 is maintained in the LBRC and can be rapidly mobilized to the cell surface during diapedesis (200). Neutrophils adherent to the endothelium have higher surface expression of CD99 than unactivated peripheral neutrophils (200). *In vivo* studies confirm the role of CD99 in leukocyte recruitment into inflamed tissue (270, 272) and into the bone marrow (273).

Similar to PECAM-1, outward-in signaling through CD99 modulates integrin avidity. Ligation of CD99 induces VLA-4 affinity/avidity changes in resting memory CD4 T-cells (274). These changes promote arrest of T-cells under flow conditions on TNF-alpha-activated endothelium or on immobilized VCAM-1 (274). T-cell arrest is blocked by anti-VLA-4 or anti-VCAM-1 antibody, but not by anti-LFA-1 or anti-ICAM-1 antibody (274). This suggests that CD99 specifically signals to VLA-4 in these cells. After CD99 engagement, T-cells flatten and spread over VCAM-1-enriched surfaces and acquire a mobile phenotype (274). In B-cells, CD99 ligation induces LFA-1-dependent cell adhesion which can be disrupted by anti-LFA-1 or anti-ICAM-1 antibody (275). In these studies, CD99 engagement resulted in a twofold increase in cell surface expression of LFA-1 within 30 minutes. However, when a splice variant of CD99 with a truncated cytoplasmic domain was over-expressed, LFA-1 expression was down-regulated and cell adhesion was abrogated. Full length CD99 contains a PKC-alpha phosphorylation consensus site that has been linked to Erk and Jnk MAPK signaling during T-cell adhesion (276, 277). Thus, CD99 activation may modulate kinase activity to promote cytoskeletal alterations, integrin affinity changes, and/or mobilization of integrins to the cell surface. Loss of this phosphorylation site could negatively regulate leukocyte adhesion. The relative abundance of full length CD99 and its splice variant in various leukocytes may serve as an important regulator of leukocyte adhesive properties, enabling the rapid adhesion/de-adhesion that is required for cellular trafficking.

3.3.5. PVR and DNAM-1

The polio virus receptor (PVR) and nectin-2 are related members of the immunoglobulin gene superfamily that are expressed on endothelial cells and regulate junctional complexes and leukocyte diapedesis. Both PVR and nectin-2 localize to interendothelial junctions (278, 279) where they contribute to barrier integrity by binding to nectin-3 on apposed cells (278, 280, 281). Nectin-2 also establishes homotypic bonds between endothelial cells (279). The cytoplasmic domains of PVR and nectin-2 contain a PDZ-binding motif that facilitates binding to ZO-1 and AF-6 scaffolding proteins (282). Through these interactions, PVR and nectin-2 become linked to the actin cytoskeleton, to JAM-A, and to tight junction and adherens junction complexes (283-285). Consequently, PVR and nectin-2 contribute to regulation of cell adhesion and barrier integrity. The predominant binding partner for PVR and nectin-2 on leukocytes is DNAM-1 (DNA accessory molecule 1) (286), another immunoglobulin gene superfamily member (287). DNAM-1 is highly expressed on most leukocytes, with the exception of granulocytes, and participates in leukocyte adhesion (286, 287). On endothelial cells, DNAM-1 binds preferentially to PVR over nectin-2 (278). Antibody blocking of either DNAM-1 or PVR reduces leukocyte transmigration by 80% and causes leukocyte arrest above intercellular junctions (278). Leukocyte adherence to the endothelium is not affected by blocking antibodies, suggesting that DNAM-1/PVR interactions specifically participate in diapedesis. As described for PECAM-1, leukocyte pseudopods are found to be minimally protruding into the paracellular space. Thus, DNAM-1/PVR may act at a similar step in transmigration as PECAM-1.

3.3.6. PrP^c

PrP^C (protease resistant protein- cellular isoform) also participates in leukocyte diapedesis across endothelial monolayers (288). PrP^C is the normal cellular isoform of the human prion protein and is constitutively expressed in the CNS (289, 290), vasculature (288, 291), and on most leukocytes (205, 292-297). Many cellular and extracellular ligands involved in leukocyte transmigration interact with PrP^C including heparan sulfate (298), laminin (299), selectins (300), and laminin receptor precursor (298, 301). In addition, PrP^C binds homotypically to other PrP^C molecules (288), providing for diverse physiological activity. PrP^C interacts with multiple binding partners as a result of its differential glycosylation (302, 303) and a flexible anchoring to cells through glycosylphosphatidylinositol (292). On leukocytes, PrP^C has been implicated in hematopoietic stem cell renewal (304), leukocyte differentiation and maturation (294, 296, 305), T cell activation and proliferation (292, 297, 306, 307), formation of immunological synapses (295, 307,

308), and regulation of phagocytic activity (309). In cerebral microvessels, PrP^C is junctionally expressed and participates in leukocyte transmigration (288). Antibody blocking of PrP^C on either leukocytes or endothelial cells reduces diapedesis by 60% (288). Therefore, PrP^C appears to have a specific role in diapedesis, but not in arrest or traverse through the basement membrane of vascular beds, as adherence to activated endothelium and chemotaxis through endothelial cell-free fibronectin and collagen matrix are not disrupted (288). Concomitant blocking of PrP^C and PECAM-1 does not result in additive reduction in transmigration, suggesting that these molecules function in similar stages of diapedesis (288).

3.4. Junctions and matrices

3.4.1. Gap junctions

An important mechanism for intercellular communication between adherent cells is through gap junctions. These are protein channels that form between two cells, with each cell contributing a hemichannel, or connexon, to the complex. Each connexon is composed of six connexin subunits, with different connexins able to form homomeric or heteromeric hemichannels (310). As a result, multiple gap junctions of varying composition and physiologic function may exist between cells (311, 312). Our laboratory demonstrated that connexin 43-containing gap junctions form between TNF-alpha- and IFN-gamma-activated primary human monocytes and endothelial cells in our BBB model (313). These interactions contribute to diapedesis, as gap junction inhibitors significantly reduced transmigration. Gap junction inhibitors also decreased the secretion of MMP-2 (matrix metalloproteinase-2) from monocytes, a protease that helps to dismantle tight junction complexes during diapedesis. These data suggest that intercellular communication, mediated by gap junctions between monocytes and endothelial cells, plays an important role in coordinating leukocyte diapedesis. Direct communication through gap junction channels may provide for rapid transduction of signals between cells without dilution in the extracellular space. Other groups have found gap junction formation between lymphocytes and the endothelium (314, 315) and a contribution of these channels to transmigration (316).

3.4.2. Tight junctions

As the leukocyte traverses the interendothelial space, it must transiently disrupt tight junctions and adherens junctions and distort the paracellular compartment physically to accommodate leukocyte transmigration. This is accomplished through signaling within endothelial cells. Tight junctions are composed of an intricate network of transmembrane and cytoplasmic proteins that are organized in caveolae and linked to the filamentous actin cytoskeleton. They provide polarity to endothelial cells and act as a major regulator of barrier permeability (317-319). The predominant membrane proteins associated with tight junctions in BMVEC are claudin-3 (320), claudin-5 (321, 322), and occludin (323, 324). Each has two extracellular loops that extend into the intercellular space (323, 325) where they interdigitate with the extracellular loops of homologous proteins on apposing endothelial cells (326, 327). Intracellular adaptor proteins zonula occludens (ZO-1 and ZO-2) link the cytoplasmic tails of claudins and occludin to the actin cytoskeleton (328-330). Additional scaffolding proteins including cingulin and AF-6 further strengthen the connection between tight junction proteins and actin through interactions with ZO-1 (331, 332). Tight junction complexes are transiently disrupted during leukocyte transmigration (317, 333). One mechanism involves ICAM-1-mediated cellular signaling. Upon leukocyte integrin engagement of endothelial ICAM-1, Rho is activated (334-337). This leads to activation of Rho kinase which causes the phosphorylation of the cytoplasmic tails of claudin-5 and occludin (338, 339). This phosphorylation results in the transient redistribution of these molecules intracellularly (340, 341). The extracellular domain of occludin is proteolytically degraded by MMPs in response to leukocyte transmigration, promoting endothelial gap formation and leukocyte diapedesis (333). Tight junction disassembly has two important effects that facilitate leukocyte transmigration. First, it physically disrupts the protein structures that impede leukocyte forward progress through the paracellular space. Second, by reorganizing the cytoskeleton, dismantling of tight junctions allows the endothelial cell to contract and physically accommodate the leukocyte in the junctional compartment.

3.4.3. Adherens junctions

The adherens junction anchors cells together and provides significant tensile strength to cellular borders. The principal protein that forms these junctions in endothelial cells is VE-cadherin (342, 343). In a calcium-dependent and homotypic manner, the extracellular domains of VE-cadherin dimerize, oligomerize, and interdigitate with VE-cadherin complexes on adjacent endothelial cells (344-349). The cytoplasmic tail of VE-cadherin is linked to the actin cytoskeleton through a complex intracellular arrangement of proteins. VE-cadherin binds three catenins: p120-catenin, beta-catenin, and gamma-catenin (350-352). Beta-catenin and gamma-catenin bind directly to alpha-catenin, which is linked to filamentous actin by alpha-actinin (353). To gain entry into the CNS parenchyma, the leukocyte must transiently disrupt the adherens junction complex (354, 355). ICAM-1 engagement by leukocyte integrins disrupts this complex by activating the kinases Src and Pyk2 (356). These kinases promote phosphorylation of both beta-catenin (153) and the VE-cadherin cytoplasmic tail at its p120- and beta-catenin binding domains (356). As a result, beta-catenin dissociates from VE-cadherin, transiently disrupts the adherens junction, promotes interendothelial gap formation, and facilitates paracellular transmigration of leukocytes (153, 356). LFA-1/ICAM-1 interactions also induce phosphorylation of focal adhesion kinase and the actin binding protein paxillin through activity of Rho GTPase (334, 335). These phosphorylation events promote endothelial cytoskeletal remodeling, stress fiber formation, and leukocyte diapedesis (334). As detailed earlier, VCAM-1 engagement has a similar effect, although signaling is mediated by reactive oxygen species and p38 MAPK activity (152, 158). Leukocyte adhesion to TNF-alpha-stimulated endothelium results in dissociation of vascular endothelial protein tyrosine phosphatase (VE-PTP) from VE-cadherin (357). VE-PTP is an endothelial-

restricted phosphatase that interacts with the membrane-proximal extracellular domain of VE-cadherin and regulates its phosphorylation (358, 359). By dephosphorylating VE-cadherin's cytoplasmic tail, VE-PTP stabilizes VE-cadherin complexes at the adherens junction and maintains barrier integrity (358). Through yet defined intracellular signaling, leukocyte arrest on the apical aspect of endothelial cells induces VE-PTP/VE-cadherin dissociation, VE-cadherin tyrosine phosphorylation, and disruption of the adherens junction. This results in increased barrier permeability and leukocyte transmigration (357).

3.4.4. Extracellular matrix

After transmigrating through the paracellular space, the leukocyte must still cross the basal lamina which is composed of a dense meshwork of proteins and proteoglycans including collagen IV, laminins, fibronectin, and heparan sulfate glycosaminoglycans. Adhesion molecules expressed on the leukocyte surface escort the leukocyte through the basement membrane and to the perivascular space. Important interactions include: (1) leukocyte integrins with collagen IV (360-362), fibronectin (360, 362-364), laminins (262, 263, 361, 363), and heparan sulfate (365) and (2) PrP^C with laminin (299, 366). Adhesion-dependent engagement of $beta_2$ integrins induces expression of $beta_1$ integrins on the leukocyte surface (360). This increases integrin interactions with basement membrane proteins and promotes leukocyte movement through the extracellular matrix (360). Heparan sulfate compounds (perlecan, agrin, and type XVIII collagen) are also important in maintaining a chemotactic gradient by binding chemokines (367, 368).

Upon entering the extracellular matrix, a leukocyte must traverse the dense protein network of the basement membrane. This is accomplished by several degradative enzymes including MMPs, heparanases, and sulfatases. MMPs are endoproteases that use zinc as a cofactor to hydrolyze peptide bonds. Many MMPs remodel the extracellular matrix including MMP-1 (collagenase) (369), MMP-2 (gelatinase) (370), MMP-9 (gelatinase) (371), and MMP-12 (elastase) (372). Heparanases are endoglycosidases which cleave oligosaccharides from heparan, disrupting binding interactions between constituents of the extracellular matrix (373). Sulfatases also contribute to remodeling of the basal lamina by hydrolyzing sulfate esters on glycosaminoglycans (374). In an activated state, leukocytes and endothelial cells express membrane-bound MMPs and heparanases or release soluble enzymes (375-379). Leukocyte engagement of matrix laminins further induces MMP expression by these cells and promotes leukocyte taxis (380). The release of several enzymes with varying specificities promotes degradation of the proteinaceous framework of the basement membrane. These proteolytic enzymes facilitate leukocyte entry into the CNS (381). However, basement membrane remodeling is a tightly controlled process and MMPs are quickly inhibited by decreased production and release and by the activity of tissue inhibitors of metalloproteinases (382). Endothelial cells, astrocytes, and pericytes all elaborate proteins that contribute to the basal lamina of the BBB. Despite MMP activity and leukocyte chemotaxis, the basement membrane is quickly reestablished such that barrier properties are not compromised.

As the leukocyte sequentially engages various adhesion molecules, not only is the leukocyte chaperoned across the interendothelial junction and through the extracellular matrix, but also cellular signals are initiated that result in opening of the tight junctions and adherens junctions and dismantling of the basement membrane at the leading edge of leukocyte migration. These interactions are complex, well coordinated, and exquisitely controlled. In non-pathologic states, leukocytes can quickly negotiate the paracellular compartment without compromise to barrier integrity. Under inflammatory conditions, transmigration is enhanced such that distinct leukocyte populations are directed into specific tissues. Multiple adhesion molecules are required for this process for at least three reasons. First, each molecule plays a role in a different step of leukocyte trafficking. Leukocyte capture and adhesion to the endothelium from a fluid stream, homing to paracellular junctions, diapedesis and disruption of junctional complexes, and traverse through the extracellular matrix are each distinct processes that require engagement and signaling through specific cellular receptors. Second, different inflammatory conditions favor the contribution of certain adhesion molecules to leukocyte transmigration over others. Third, adhesion molecules are differentially expressed on leukocyte subsets, and thus contribute to the transmigration of specific leukocyte populations. Collectively, the reliance of leukocyte transmigration on many cell adhesion molecules enables the precise regulation of which leukocyte is able to be recruited into specific tissues under distinct inflammatory states.

3.5. Transcellular diapedesis

In addition to paracellular transmigration of leukocytes between endothelial cells, transcellular movement of leukocytes through individual endothelial cells has been described for many classes of cells including monocytes, neutrophils, and T-cells (185, 186, 196, 383, 384). Not all leukocytes demonstrate the same preference for route of transmigration across the endothelium. Studies conflict; and this may be due differences in the vascular bed from which endothelial cultures are derived and whether endothelial cells are activated. Several studies demonstrate that monocytes and neutrophils transmigrate predominantly by the paracellular route (185, 385), while lymphocytes show an increased ability to travel transcellularly (385). However, other groups found polymorphonuclear cells (PMNs) to use transcellular diapedesis preferentially through activated human umbilical vein endothelial cells (186, 196), while T-cells exclusively transmigrate through the paracellular space (186). This may partially be a function of differential expression of cell adhesion molecules by leukocyte and endothelial cell subsets, and/or of chemokine specificity, and may depend on what signaling cascades are activated and suppressed in both cell types.

During adhesion, leukocytes induce the formation of docking structures in endothelial cells called transmigratory cups. These structures surround the leukocyte with projections rich in the adhesion proteins ICAM-1 and VCAM-1; cytoplasmic proteins ezrin, radixin and moesin; and cytoskeletal proteins vinculin, talin and alpha-actinin (184, 185). The transmigratory cup chaperones a cell either between the paracellular space or through the endothelial cell (185). Endothelial ICAM-1 plays an active role in determining whether leukocytes use the paracellular or transcellular route. Ligation of ICAM-1 triggers cytoplasmic signaling events that lead to ICAM-1 clustering and the translocation of apical ICAM-1 to caveolae and F-actin-rich regions, and to the eventual transport of ICAM-1 with caveolin-1 to the plasma membrane (384). This contributes to formation of channels through which leukocytes migrate (384). By knocking down caveolin in endothelial cells, it was demonstrated to be required for transcellular, but not paracellular transmigration (384). Use of a small peptide inhibitor of the cytoplasmic tail of ICAM-1 was also shown to preferentially reduce transcellular migration (186). These findings suggest a requirement of ICAM-1 localization to caveolae and specific signaling mediated by ICAM-1 for transcellular diapedesis. ICAM-1 surface density and distribution, as well as endothelial cell shape, also contribute to transcellular transmigration of leukocytes (186). Increased endothelial ICAM-1 favors transcellular diapedesis of PMNs, as does an elongated, rather than polygonal, shape to the endothelium. This may facilitate localization of leukocytes to areas away from cellular junctions.

Leukocytes also actively participate in transcellular diapedesis. Leukocytes extend a podosome rich in LFA-1 and talin-1 into the endothelium which is accommodated by ICAM-1-enriched endothelial invaginations, termed a podoprint (386). Leukocyte podosomes invade deeply into endothelial cells, nearing the basal membrane, and are termed invadopodia. Podosomes induce recruitment and fusion of endothelial vesicles to the plasma membrane of the podoprint, forming transcellular pores, or channels through which the leukocyte travels. Formation of these channels is dependent upon SNARE complex formation, but not involvement of caveolae or endosomes. Thus, formation of the transmigratory cup and podoprint are two distinct processes. Transcellular pore formation actively distorts the endothelial cell, displacing cytoplasm, actin, microtubules, and endoplasmic reticulum, but not the nucleus. It has been suggested that leukocytes actively extend podosomes into the endothelial cell as they laterally travel across the vascular bed, looking for sites of least resistance, either at the paracellular space or within an endothelial cell. If an area of the endothelial cell provides a low level of cytoplasmic and organelle-mediated resistance, then transcellular pores may form and facilitate transcellular migration (386).

Some studies suggest that the transcellular route, under certain conditions, may be particularly relevant in organs that have extremely tight endothelial junctions, such as the brain (387). There are no direct studies of the pathway virally-infected cells use to cross the BBB. In retroviral-associated diseases such as HIV-1-associated dementia (HAD) and human T-cell leukemia virus (HTLV-1)-associated myelopathy/tropical spastic paraparesis, the penetration of virus into the CNS and subsequent BBB damage and dysfunction are mediated, in part, by either infected monocytes or lymphocytes that transmigrated across the BBB. It was recently demonstrated that co-culture of HTLV-1-infected lymphocytes induces an increase in their transendothelial transit (388), and infection of endothelial cells with HTLV-1 results in decreased barrier function due to an increase in BBB permeability and lymphocyte transmigration (389). Preliminary data from our laboratory suggest that freshly isolated and stimulated, uninfected monocytes and T-cells preferentially use the paracellular route. In contrast, HIV-1-infected cells cross transcellularly (Buckner, C.M., unpublished data). Thus, infection of leukocytes or endothelial cells with pathogens may also influence the route of transmigration.

4. MODELS OF LEUKOCYTE TRANSMIGRATION

As previously described, the BBB is a dynamic interface between the blood and the CNS. Several *in vitro* models are used to study BBB function in the context of disease and to screen drugs targeted to the CNS. Blood-brain barrier modeling is also fundamental to studying leukocyte transendothelial migration, which is enhanced in HIV-1 infection.

The first *in vitro* model of the BBB was established after successful isolation of rat brain microvessels (390). This type of model uses monocultures of brain endothelial cells grown on a porous membrane that divided a culture chamber into two compartments representing the blood and the brain (391-393). However, it was recognized that culture of brain endothelial cells alone leads to loss of phenotype of the enzyme gamma-glutamyl transpeptidase (gamma-GT). Communication between cells of the BBB is crucial for the formation and maintenance of a functional BBB (394, 395). Astrocytes regulate brain endothelial characteristics and function, as well as induce the formation of interendothelial tight junctions (394, 396, 397). A number of *in vitro* BBB models are thus composed of brain endothelial cells co-cultured with astrocytes. Some use cells from different species such as bovine, porcine, rat, mouse, and human, while others are syngeneic (32, 398-407). We developed and characterized a model of the human BBB in which human fetal astrocytes and human umbilical vein endothelial cells or BMVEC are cultured on opposite sides of a tissue culture insert. The inserts have 3.0 micron pores that allow astrocyte foot processes to penetrate the insert and establish contact with the endothelial cells. Endothelial cells in our co-culture system express the BBB-specific markers gamma-GT and GLUT-1 (glucose transporter-1) and form junctional complexes (401). We used this model to examine the mechanisms of both uninfected and HIV-1-infected monocyte and lymphocyte transmigration across the BBB in response to the chemokine CCL2 (402). We also examined the impact of HIV-1 proteins on barrier permeability. Current studies in our laboratory use this model to identify the phenotype

of the monocyte crossing the BBB and the effects of drugs of abuse on the BBB in the context of neuroAIDS (Buckner, C.M., unpublished data; Calderon, T.M., unpublished data).

Models of the BBB also include BMVEC cultured with enriched media. Some models grow BMVEC with glia-conditioned media because soluble factors released by glia or glioma cells are believed to participate in the induction of the BBB phenotype (408-410). Removal of astrocytes from BMVEC cultures leads to an increase in permeability to sucrose and peroxidase (411). However, the increase in junctional permeability does not alter occludin, claudin-3, claudin-5, ZO-1, or ZO- 2 immunostaining (411). This emphasizes that disruption of tight junctions, as measured by fluorescent intensity and localization of paracellular markers, does not necessarily indicate functional loss of tight junctions. Other models culture BMVEC with cyclic adenosine monophosphate or glucocorticoids, such as hydrocortisone and dexamethasone, to enhance barrier properties (412-414). Most of these studies were performed in rodent models. We found human astrocyte-conditioned media does not enhance the BBB properties of our model; only human astrocytes in co-culture with endothelial cells result in barrier properties (401).

Immortalized brain endothelial cell lines have been generated to overcome difficulties with access to human tissue, low yield of cells, and concern about the quality of tissue obtained from autopsy or surgical specimens. Immortalized cell lines often allow for easy, reproducible *in vitro* BBB models. To evaluate drugs that gain entry to or are excluded from the brain, a humanized dynamic *in vitro* BBB model (hDIV-BBB) was developed (415). A human BMVEC cell line (HCMEC/D3) was grown in the lumen of hollow microporous fibers and exposed to a physiological pulsatile flow. This model demonstrated greater maintenance of *in vitro* BBB physiological permeability properties even in the absence of astrocytes (415). Other immortalized cell models are composed of cells from different species, syngeneic astrocytes, and/or cell lines (409, 416-419).

Few data exist on the effects of neurons and pericytes on *in vitro* BBB models. Co-culture of RBE4 cells, a rat brain endothelial cell line, with rat primary neurons decreases transmonolayer dopamine flux (420), while thin brain slices cultured over BMVEC monolayers on a permeable membrane result in similar resistance to dopamine permeability (421). Pericytes stabilize the brain capillary structure (422, 423) and have been implicated in the development, maintenance, and regulation of the BBB (395, 422). Similar to astrocytes, pericytes tighten the paracellular barrier in cultured brain endothelial cells (424, 425). A triple co-culture model consisting of rat brain endothelial cells and pericytes grown on the opposite sides of a porous membrane and cultured in the presence of astrocytes can also be used as a tool for research on BBB physiology and pathology (426, 427).

The major criterion for all BBB models is that they must display restrictive paracellular pathways and selective transcellular permeability. Most cell culture models of the BBB use primary or immortalized BMVEC. The endothelial cells are co-cultured with astrocytes, pericytes, both cell types, or cell products. Since the late 1970s, *in vitro* models of the BBB from different mammalian species have been developed, making their comparison difficult. It is important to have experimental tissue culture models to understand the pathophysiological behavior of the BBB. These models enable the study of trafficking of leukocytes, virus, other pathogens, or drugs into the CNS and the design of protective and therapeutic approaches to inhibit access across the BBB. The data generated from these *in vitro* systems, while highly valuable, must be carefully interpreted in the context of human disease.

5. HIV-1 DYSREGULATION OF LEUKOCYTE TRANSMIGRATION AND OF THE BLOOD-BRAIN BARRIER

5.1. Viral infection

HIV-1 infection results in not only immune dysfunction but also CNS metabolic derangement. Pathologic hallmarks of HIV-1 brain infection include abnormal accumulation of monocytes/macrophages in the perivascular space and parenchyma (17, 37, 428, 429) and increased permeability of the BBB (32, 33, 338, 339, 430). Thus during HIV-1 infection, the homeostatic mechanisms that control monocyte transmigration across the BBB are dysregulated. These changes are mediated by a complex interplay between the effects of HIV-1 infection, viral proteins, and abnormal cytokine and chemokine production on leukocytes and on the BBB.

When monocytes/macrophages become infected with HIV-1, they increase their production and release of CCL2 (431-433), the most potent chemoattractant for monocytes (434-436). CCL2 acts in an autocrine manner to enhance viral replication and release in the infected monocyte/macrophage (25). CCL2 released by infected monocytes, macrophages, microglia, and astrocytes also creates a chemotactic gradient, recruiting additional monocytes to sites of inflammation and promoting monocyte entry into the CNS. Additionally, our laboratory demonstrated that HIV-1 infection maintains monocyte expression of CCR2, the receptor for CCL2, on the cell surface (402). This allows the monocyte to be more responsive to CCL2. Combined, the effects of HIV-1 on the monocyte promote chemotaxis and viral virulence.

In a tissue culture model of the BBB, our laboratory demonstrated that HIV-1-infected monocytes have an increased capacity to transmigrate in response to the chemokine CCL2 as compared to uninfected cells (402). This appears to be CCL2-dependent, as HIV-1 infection alone does not significantly alter monocyte transmigration and other monocyte chemoattractants do not recruit infected monocytes to the same extent. In addition, HIV-1 and CCL2 synergize to selectively recruit monocytes across tissue culture models, as T-cells, while increased, do not demonstrate the same proportional increase in transmigration (402). Thus HIV-1, particularly

R5-tropic strains, appears to promote a migratory phenotype in monocytes.

HIV-1-infected monocytes induce expression of cell adhesion molecules in BMVEC. Both E-selectin and VCAM-1 are up-regulated in BMVEC when co-cultured with HIV-1-infected monocytes (437). This occurs when infected monocytes are in direct contact with BMVEC and when monocytes are separated from BMVEC by a transwell filter that enables diffusion of soluble mediators between the two cell types. HIV-1 encephalitic (HIVE) brain tissue shows a correlation between increased TNF-alpha and IL-1beta levels and elevated E-selectin and VCAM-1 (437). Since BMVEC expression of E-selectin and VCAM-1 are known to be induced by TNF-alpha and IL-1beta (139, 438-441) and HIV-1-infected monocytes are known to be a source of these cytokines (9, 24, 442), these findings support a mechanism by which TNF-alpha and IL-1beta, released by HIV-1-infected monocytes, cause increased expression of E-selectin and VCAM-1 on BMVEC. Other studies found that cerebral microvessels associated with HIV-1 p24-positive perivascular monocyte infiltrates in HIVE brains have a similar increased expression of E-selectin and VCAM-1 (437). Furthermore, when BMVEC are isolated from HIVE tissue and cultured with uninfected monocytes, avid binding of the monocytes to the endothelium is observed as compared to weak binding of monocytes to uninflamed endothelium with diminished expression of E-selectin and VCAM-1. Antibody blocking of E-selectin and VCAM-1 abrogates the enhanced binding of monocytes to HIVE endothelium (437). This is consistent with studies in SIV (simian immunodeficiency virus) models of encephalitis where elevated levels of VCAM-1 are associated with efficient monocyte transmigration (443, 444). Taken together, these studies clearly support a role for HIV-1 in enhancing the migratory capacity of monocytes across the BBB.

HIV-1 infection also dysregulates leukocyte adhesion molecules. Monocyte LFA-1 and LFA-3 are both up-regulated upon infection with HIV-1 and this promotes increased adherence to BMVEC (445). The enhanced affinity of the infected monocyte for the endothelium can be disrupted by blocking either LFA-1 or its ligand, ICAM-1, with antibody. Our laboratory found that HIV-1-infected PBMCs (peripheral blood mononuclear cells) increase their expression of PECAM-1, CD99, JAM-A, and occludin when compared to uninfected cells (Eugenin, E. A., unpublished data). We also demonstrated that CCL2 treatment induces HIV-1-infected PBMCs to shed PECAM-1. We found sera levels of soluble PECAM-1 to be elevated in HIV-1-infected individuals and that sPECAM-1 accumulates in the CNS parenchyma and vasculature of individuals with HIVE (446). The increased expression of adhesion molecules on HIV-1-infected PBMCs may enhance their ability to transmigrate across the BBB, while shed PECAM-1 may compete for binding to membrane-bound PECAM-1 in the paracellular space, disrupting barrier integrity and facilitating leukocyte CNS entry.

Nitric oxide (447) and superoxide (448) are produced by HIV-1-infected phagocytes and have multiple effects that favor monocyte transmigration and BBB disruption. Uninfected monocytes produce little NO (447). However, the NO produced by HIV-1-infected monocytes can act in an autocrine and paracrine manner to induce hyperactivation of monocytes (449). Exposure to NO also enhances viral replication in macrophages (450). Activated monocytes produce high amounts of NO (447), are more permissive to viral replication (451), and up-regulate their expression of cell adhesion molecules (452). In addition, nitric oxide combines with superoxide to form peroxynitrite, which irreversibly nitrates tyrosine residues on proteins (453) and disrupts endothelial monolayer integrity (454, 455). Because PKC activity is required for tight junction assembly (456), it has been suggested that the disruption of endothelial barrier properties associated with peroxynitrite may be due to altered phosphorylation of tight junction proteins. Thus, the cycle of monocyte/macrophage infection with HIV-1, NO production, and monocyte/macrophage activation not only compounds the spread of virus among monocytes/macrophages and the release of NO into tissue, but also enhances the ability of monocytes to gain entry into the CNS across the BBB.

HIV-1-infected monocytes/macrophages and microglia also have increased expression and secretion of the proteolytic enzymes MMP-1 (457), MMP-2 (29, 457), MMP-3 (457), and MMP-9 (445, 457, 458). These enzymes contribute to extracellular matrix degradation. Co-culturing infected monocytes with endothelial cells causes monolayer disruption and increased permeability to albumin (445). Loss of monolayer integrity can be reversed with addition of the MMP inhibitors TIMP-1 and TIMP-2 (tissue inhibitor of metalloproteinase) (445). These *in vitro* studies are supported by the finding that perivascular and parenchymal phagocytes express high levels of MMPs in HIVE tissue (457) and that MMP CSF levels correlate with markers of BBB breakdown including elevated CSF/serum albumin ratios and mononuclear cell migration into the CNS (459, 460).

Similar to monocytes, HIV-1 infection of T-cells is associated with a migratory phenotype. CD8 T-cells isolated from CSF have increased expression of the adhesion molecules LFA-1 and VLA-4 and of the chemokine receptors CXCR3 and CCR5 as compared to peripherally isolated T-cells (461). This is in agreement with leukocyte infiltrates characteristic of other neuroinflammatory conditions including multiple sclerosis and meningitis (462). Increased LFA-1 expression in HIV-1-infected peripheral T-cells has been demonstrated by several groups (463-465). HIV-1 infection of CD4 T-cells is associated with increased surface expression of CCR5, while CXCR4 expression on CD8 T-cells is decreased in response to infection (466). This may not only favor infection with R5 tropic HIV-1 strains, but also affects the response of these T-cell populations to chemotactic stimulation. CCL3, CCL4, and CCL5 are all ligands for CCR5 (467) and are elevated in the CSF of HIV-1-infected individuals (468). This suggests that HIV-1 infection promotes the recruitment of T-cells into the CNS by increasing the expression of the chemokine receptors and adhesion molecules necessary to traverse the BBB.

However in our model of the BBB, we do not detect increased transmigration of HIV-1-infected T-cells in response to CCL3 or CCL5 (402).

Transmigration of HIV-1-infected leukocytes across tissue culture models of the BBB in response to CCL2 is also associated with increased barrier permeability. Our laboratory demonstrated that occludin, claudin-1, and ZO-1 all exhibit decreased localization at tight junctions and diminished whole cell expression after 24 hours of CCL2-mediated diapedesis of infected PBMCs (402). In addition, after CCL2-mediated transmigration of HIV-1-infected PBMCs, endothelial cells and astrocytes from our tissue culture model had increased immunostaining for MMP-2 and MMP-9. These data suggest that HIV-1 infection of leukocytes disrupts the homeostatic mechanisms that regulate their transmigration across the BBB and the maintenance of barrier integrity.

5.2. Viral proteins

Viral proteins have important effects on leukocyte trafficking and barrier permeability (Table 3). Tat is a viral protein required for HIV-1 gene expression and replication that is found in high levels in the serum (469) and brain parenchyma (470-473) of individuals with HIVE and HIV-1-associated neurocognitive disorder (HAND). Tat is actively released from infected cells (474), is able to bind many cellular and extracellular proteins (474-476), can efficiently enter many cell types (477-479), affects cellular signaling (480-482), and regulates host gene expression (429, 482-491). Thus, tat promotes multiple pathological processes in the CNS (492-495). In endothelial cells, tat induces expression of E-selectin (472, 496, 497); while in endothelial cells, monocytes/macrophages, microglia, and astrocytes, ICAM-1 and/or VCAM-1 are increased in response to tat (429, 491, 496, 497). The tat-mediated up-regulation of cell adhesion molecules enhances the ability of leukocytes to adhere to the endothelium and to transmigrate into the brain parenchyma (429, 491, 496).

Tat itself is chemotactic (492, 498, 499), but also increases the production of CCL2 and other chemokines by endothelial cells (429, 481, 500), astrocytes (429, 501-505), and microglia (429, 482, 506, 507). The release of CCL2 recruits circulating leukocytes into the CNS, disrupts barrier integrity, and promotes metabolic dysfunction (481, 508). In addition, tat directly alters endothelial monolayer permeability and compounds the CCL2-mediated effects on barrier properties (480, 509). Tat treatment of BMVEC induces phosphorylation and activation of focal adhesion kinase which promotes reorganization of the cytoskeleton, cellular migration, and changes in barrier permeability (480). *Ex vivo* studies of BMVEC from tat-expressing transgenic mice confirm a tat-associated disruption of BBB integrity (480). Tat-injected mice have BBB disruption and excessive monocyte recruitment into the CNS (508). Tat also induces nitric oxide production by BMVEC (509) and astrocytes (510) through the activation of inducible nitric oxide synthase. Increased nitric oxide levels correlate with BMVEC apoptosis and barrier dysfunction (509). Furthermore, tat induces macrophage (511) and astrocyte (D'Aversa, T.G., unpublished data) production of MMP-2 and MMP-7, which is associated with degree of neuronal loss and severity of neurobehavioral impairment in mice (511). Collectively, the tat-mediated effects on CNS cell adhesion molecule expression, chemokine production, MMP production, and BBB permeability promote leukocyte and viral entry into the CNS and contribute to metabolic encephalopathy.

Gp120 is an HIV-1 glycoprotein expressed on the viral envelope that allows for receptor-mediated entry of HIV-1 into CD4 expressing cells (512-514). It is found in high levels in the serum (515) and brain parenchyma (516) of individuals with HIVE and HAND. In addition to being expressed on free virus, gp120 is shed into the cellular environment (517). The interaction of gp120 with endothelial cells, astrocytes, and microglia induces increased expression of ICAM-1 (518-522), while VCAM-1 is also up-regulated on BMVEC (521). This promotes leukocyte adherence to cerebral microvessels and entry into the CNS (520, 521). Additionally, gp120 alters endothelial properties and some studies have shown it to be directly cytotoxic to endothelial cells in culture (523). Expression of occludin, ZO-1, and ZO-2 is reduced by gp120. This compromises barrier integrity through the gp120-mediated activation of PKC and subsequent activation of myosin light chain kinase and cytoskeletal rearrangement (523). Gp120 also induces secretion of inflammatory mediators such as IL-1beta, TNF-alpha, and NO from glia and phagocytes which facilitate leukocyte chemotaxis and BBB disruption (524-526).

Nef is a nonstructural HIV-1 protein that is involved in viral budding and is also found in high levels in the brain parenchyma of individuals with HIVE and HAND (19, 21, 22, 527, 528). The expression of nef by astrocytes promotes their release of chemokines, particularly CXCL10 (528) and CCL2 (529). Nef is also directly chemotactic for monocytes (530-532) and, when in the presence of tat, promotes T-cell recruitment (533). In addition, nef induces the release of CCL3 and CCL4 from macrophages, thereby activating resting T-cells, enhancing their adhesion to endothelium, and promoting their chemotaxis (534, 535). The interaction of nef with monocytes/macrophages induces MMP-9 release and subsequent loss of endothelial barrier integrity (536). Several viral proteins that are associated with intact virus or are released into the extracellular space promote leukocyte adherence to brain microvascular beds and their subsequent entry into the brain parenchyma. By altering endothelial tight junction assembly and cytoskeletal arrangement, viral proteins also disrupt the BBB and facilitate the transmigration of leukocytes into the CNS.

5.3. CCL2

The presence of HIV-1 in the CNS promotes cytokine and chemokine dysregulation (537) that can have profound effects on the integrity of the BBB (341, 538, 539). Important sources of CCL2 include endothelial cells (429, 481, 540), and activated or infected astrocytes (429, 501-504, 541), microglia (429, 482, 506), and monocytes/macrophages (431). In cultures of mouse

BMVEC, CCL2 alters monolayer permeability. Both occludin and ZO-1 whole cell protein expression, cell junction localization, and cytoskeletal association are decreased in response to CCL2 (539). ZO-2 and claudin-5 are also redistributed away from tight junctions in a CCL2-dependent manner (340, 538) which has been shown to be mediated by the activation of Rho kinase by the GTPase Rho A (340, 341). Rho kinase activity promotes phosphorylation of the cytoplasmic tail of occludin and claudin-5 and promotes disassembly of their protein complexes (338-340). Loss of tight junctions and cellular retraction, in response to CCL2, result in increased monolayer permeability as demonstrated by increased ^{14}C-inulin flux and diminished transendothelial resistance (341, 538). In addition, immunostaining demonstrates formation of gaps between confluent cells, segmental tight junction staining, and loss of the cortical actin ring (341). The destabilization of tight junctions is associated with increased monocyte transmigration and can be prevented with Rho A or Rho kinase inhibitors (339, 542).

Mouse BMVEC also express high levels of MT1-MMP (membrane type 1-matrix metalloproteinase) in response to CCL2 (543). MT1-MMP activates soluble extracellular MMPs which cause proteolytic degradation of occludin and claudin-5. This results in tight junction disassembly and alteration in BBB permeability (544). Thus in concentrations found in HIV-1-infected individuals, CCL2 can have profound effects on the permeability of endothelial monolayers and presumably the BBB. As a consequence of tight junction disassembly and cytoskeletal contraction, transmigration of leukocytes may be expedited.

Our laboratory found significant CCL2-induced changes to the adherens junction in human BMVEC. We find that endothelial junctional integrity is transiently disrupted in response to CCL2. Human BMVEC retract in a Src-dependent manner and this is associated with focal adhesion kinase activation, VE-cadherin and beta-catenin phosphorylation, and disassembly of the adherens junction. PECAM-1 acts as a beta-catenin sink, sequestering beta-catenin from the adherens junction during disassembly. This, along with CCL2-mediated activation of Akt, reduces the proteosomal targeting of beta-catenin, facilitating a rapid reconstitution of the adherens junction (Roberts, T.K., manuscript in preparation).

We also find CCL2 modulates human BMVEC matrix adhesion, migration, and proliferation genes, several of which have not been demonstrated previously to be expressed by BMVEC. Using cDNA microarray analysis of untreated and CCL2-treated human BMVEC, we find CCL2 consistently causes differential changes in the expression of 32 genes on the cDNA array in three independent experiments (Table 5). These include genes coding for signaling molecules, transcription factors, and proteins involved in cell adhesion and migration. Among these genes, astrotactin and ADAM23 are of particular interest. Astrotactin is a neuron cell surface antigen that mediates neuron-astroglial contact (545). Targeted disruption of the astrotactin gene in neurons results in: decreased ability of granule cells to bind glia, decreased rate of cell migration, abnormal granule and Purkinje cell morphology, and poor balance and coordination (546). Astrotactin had not been found previously to be expressed by endothelial cells. We hypothesize that astrotactin may play a role in the interaction of astrocyte foot processes with BMVEC, thereby contributing to BBB integrity. ADAM23 belongs to the ADAM (a disintegrin and metalloprotease) protein family, is mainly expressed in the brain, is involved in cell-to-cell and cell-to-matrix adhesion, and has been reported to be dysregulated in many cancers (547-551). To date, there are few published studies investigating these two proteins. Ongoing studies in our laboratory will determine their role in BBB integrity, infiltration of HIV-1 infected cells into the CNS, and the subsequent pathology characteristic of neuroAIDS.

HIV-1-mediated increase of CNS CCL2 additionally contributes to activation and chemotaxis of cells. CCL2 is associated with increased recruitment of leukocytes into the human CNS (552), into the CNS of SIV-infected macaques (a primate model of human HIV disease processes) (553, 554), and across tissue culture models of the BBB (402, 555). As recruited leukocytes in the CNS are a major source of virus and inflammatory and neurotoxic substances, CCL2 production compounds the neuroinflammatory cascade associated with neuroAIDS. We demonstrated that CCL2 also induces activation and chemotaxis of microglia (506). Microglial nodules are a hallmark finding in the HIV-1-infected brain and form as a result of microglia aggregation in areas of viral infection or inflammation (17, 556). Furthermore, a specific polymorphism in the CCL2 gene increases the neuroinflammatory response to HIV-1 and is associated with a severe clinical phenotype (557). Individuals homozygous for the MCP-1 allele (2578G) are more resistant to HIV-1 infection. A 50% reduction in susceptibility has been reported in adults (557). However once infected, individuals with this genotype produce elevated levels of CCL2, have a more robust recruitment of leukocytes into the CNS, and have a 4.5 fold increased susceptibility for developing HAD (557). The 2578G promoter polymorphism confers efficient transcriptional activity and increases cellular CCL2 production (557). Consequently, serum and CSF levels of CCL2 rise, viral replication is enhanced, and there is increased monocytic infiltration into the CNS (557, 558). CSF CCL2 levels correspond with genotype: homozygous G/G is associated with the highest levels, heterozygous G/A has intermediate CCL2 expression, and A/A demonstrates low CCL2 levels in the CSF (558). Homozygous individuals experience a more progressive and accelerated disease course (557). All of these findings demonstrate that CCL2 induces significant dysregulation of the CNS cellular and metabolic environment.

The complex mechanisms that mediate HIV-1's impact on leukocyte transmigration across the BBB are beginning to be understood. Viral infection, viral protein, cytokine, and chemokine effects on leukocytes, glia, and the BBB all synergize to promote leukocyte transmigration

Table 5. Effects of CCL2 on gene regulation in brain microvascular endothelial cells

Accession Number	Log Ratio	Gene Name
Cell-to-Cell Signaling and Interaction & Cellular Growth and Proliferation		
H11006	1.08	ADAM metallopeptidase domain 23
AA969184	-2.04	ankyrin repeat domain 1 (cardiac muscle)
AA400378	0.95	chromosomal 21 open reading frame 91
AA706987	-1.77	UDP-N-acetyl-alpha-D-galactosamine: polypeptide N-acetylgalactosaminyl transferase 1
AA627448	0.97	heat shock 70 kDa protein 4
AA598577	-2.27	interleukin 13 receptor, alpha 1
AA463610	-2.99	integrin, alpha 2 (CD49B, alpha 2 subunit of VLA-2 receptor)
BE935831	-2.38	microtubule associated protein 1B
AA418293	0.97	ribosomal protein L37
R16069	1.25	ribosomal protein L36
T74606	-1.8	translocation associated membrane protein 2
W72798	-1.96	zinc finger, NFX1-type containing 1
AA666098	1	astrotactin 1
Cell Cycle, Cellular Assembly, and Organization		
NM_004459	-1.74	bromodomain PHD finger transcription factor
H17882	-2.64	kallman syndrome 1 sequence
AA456299	1.05	KH domain containing, RNA binding, signal transduction associated 3
AA488672	-1.51	kruppel-like factor 7
AI679787	1.24	methyl-CpG binding protein 2
AA621202	1.95	mitochondrial tumor suppressor 1
NM_004553	0.91	NADH dehydrogenase (ubiquinone) Fe-S protein 6, 13 kDa
AA459896	1.05	SET domain containing 1A
AA496809	-1.87	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 1
NM_003074	1.64	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily c, member 1
NM_015136	0.99	stabilin 1
AA187679	1.11	tubby like protein 4
T70413	-1.7	X (inactive) specific transcript
AA707234	1.05	proline rich transmembrane protein 2
T40899	0.96	proline rich 4
Antigen Presentation, Cancer, Cardiovascular Disease		
AI004486	1	A kinase (PRKA) anchor protein 3
AA252968	1.01	annexin A8-like 2
T68710	0.93	ankyrin repeat and SOCS box containing 1
H51042	-1.95	BAT2 domain containing 1
AU117505	1.43	calreticulin
NM_000742	1.01	cholinergic receptor, nicotinic, alpha 2 (neuronal)
AA428454	1.04	keratin 10
AA133469	1.07	keratin 20
AA132946	0.99	lipase, member H
AA136016	-1.73	oxysterol binding protein-like 8
AA936434	-1.96	transcription factor 4
AA669055	1.16	major histocompatibility complex class II, DQ beta 1

and loss of barrier integrity. Once HIV-1-infected leukocytes gain entry into the brain, a self-perpetuating neuroinflammatory environment is established. The toxic and excitatory damage to neurons is compounded by continued inflammation and viral shedding. Our laboratory and others demonstrated that tat induces high levels of apoptosis in cultured human neurons (559). The resulting progressive neuronal damage results in neurocognitive impairment in a significant number of individuals. Therapeutics which disrupt the viral life cycle, neuroinflammation, and neuronal stress have been developed. Additional strategies potentially include targeting cell adhesion molecules and chemokines and their receptors with the specific goal of diminishing leukocyte recruitment into the CNS and reducing the viral, inflammatory, and neurotoxic burden.

6. THERAPEUTIC STRATEGIES

6.1. Challenges to treatment

Therapeutic treatment of the HIV-1-infected brain is complicated by many factors (Table 6). HIV-1 enters the CNS early during primary infection and induces chronic toxic and inflammatory damage to neurons, supporting glia, and the BBB throughout the lifetime of an individual (4, 560-567). However, antiretroviral therapy regimens are generally indicated only after an individual's CD4 T-cell count has fallen below 350 cells/mm^3 (568). Thus, clinically silent CNS damage may accumulate for many years before therapy is initiated. It remains unknown if there is a threshold of damage that must be reached before a clinical phenotype is recognized or how the duration of indolent, low level CNS damage affects disease outcome. In addition, it is not known if the implementation of uninterrupted ART or adjuvant therapies at CD4 T-cell levels above 350 cells/mm^3 would have an effect on the incidence or progression of HAND.

An obstacle to targeting CNS viral reservoirs and inflammatory processes is the relatively low penetration of most therapeutics across the BBB (Table 7) (569). Several factors contribute to poor CNS bioavailability including: the impermeability of the BBB, the generally poor lipophilicity of most agents used to treat HIV-1 infection, efflux transporters on BBB endothelial cells, and sequestering of drug by competitive binding to protein. The BBB is an effective anatomic barrier to the paracellular diffusion of therapeutic agents into the CNS. Junctional

Table 6. Challenges to treatment of HIV-1-associated neurocognitive impairment

HIV-1 Concern	Challenges to Treatment
early entry of HIV-1 into CNS	neurological damage before clinically apparent impairment or diagnosis of HIV-1 infection
viral reservoirs	inaccessibility to latent HIV-1 in leukocytes and immunoprivileged tissue
low blood-brain barrier penetration of many HIV-1 therapeutics	difficulty targeting CNS HIV-1, neurotoxins, and inflammation with therapeutics subtherapeutic levels may provide selective pressure for development of drug-resistant HIV-1 strains
drug toxicities associated with HIV-1 therapies	limits dosage, duration of use, or use altogether and may precipitate additional medical comorbidities
immune reconstitution inflammatory syndrome (IRIS)	results in extreme, rapidly progressive, and potentially lethal neuropathological damage and injury to CNS

proteins, tight junctions, and adherens junction complexes collectively retard the movement of large polar molecules between endothelial cells. Those molecules which are sufficiently lipophilic may be able to diffuse through the plasma membrane into capillary endothelial cells. However many of these agents, particularly antiretroviral drugs, are actively exported from endothelial cells by the P-glycoprotein drug efflux transporter or by probenecid-sensitive efflux transporters (100, 101, 103, 570-574). Those agents that do gain access to the CNS parenchyma are then susceptible to competitive binding by protein on the cell surface and in the extracellular matrix. Additional P-glycoprotein transporters are found on astrocytes, macrophages, and microglia, and in HIVE, are highly expressed (575, 576). Thus, drug distribution and establishment of an effective CNS concentration may be substantially reduced. The degree of vascularity and distance from vessels in certain anatomical regions additionally contribute to the heterogeneous distribution of pharmaceutics within the CNS. The resulting CNS subtherapeutic concentrations are thought to provide selective pressure for the development of drug-resistant viral strains.

An unpredictable challenge to HIV-1 therapy is the exacerbation of neuroinflammation that results from ART-mediated rebound of leukocyte populations. A consequence of re-establishing CD4 T-cell populations in some immunosuppressed individuals is development of a severe form of leukoencephalopathy called immune reconstitution inflammatory syndrome (IRIS) (577-582). This condition generally occurs after initiation of ART in individuals with CD4 levels below 200 cells/mm^3 and is difficult to predict (578, 582). IRIS is thought to result from the robust immune activation that follows restoration of leukocyte populations and is associated with intense monocyte/macrophage and CD8 T-cell CNS infiltration (578-580). The predominant theory is that an exaggerated immune response occurs to latent pathogen antigens present in the CNS, particularly JC virus, varicella zoster, and herpesviruses (582, 583). This results in local demyelination and edema at multiple foci and presents as a leukoencephalopathy that can be rapidly progressive, acutely debilitating, and lethal. Thus, in some individuals, ART-associated immune reconstitution results in extreme immunopathological injury to the CNS.

6.2. Antiretroviral agents

Antiretroviral therapy is the cornerstone of HIV-1 treatment. Several classes of antiretrovirals exist including agents that interfere with viral entry into the host cell, viral integration into the host genome, viral genome transcription, and viral assembly (Table 7). Combination ART has successfully reduced the incidence of frank dementia among HIV-1-infected individuals (584). Many regain substantial cognitive function, however a considerable amount of cognitive deficit frequently persists (585, 586). Some CSF markers of immune activation such as pleocytosis normalize with ART (560, 587, 588), although continued elevation of neopterin, CCL2, and sTNFR (soluble TNF-alpha receptor) suggests that baseline CNS immunoactivation continues during therapy (589-593). Viral strains resistant to antiretroviral treatment are rapidly emerging and are promoting resurgence in the incidence of HIV-1-associated leukoencephalopathy (594). The prevalence of lesser forms of neurocognitive impairment is expanding among HIV-1-infected individuals, suggesting that suppression of viral replication as a solitary treatment strategy for HIV-1-mediated neurocognitive impairment is insufficient. Thus, adjuvant therapies directed at reducing the effects of HIV-1-mediated pathological processes in the CNS rather than directly targeting viral replication, have been pursued. A few agents have been tested in clinical trials, however no therapy has been shown to alter disease outcome (595). These therapies might have greater success if implemented at the earliest signs of neuroinflammation or neurodegeneration as evidenced by CSF sampling and neuroimaging. Substantial research efforts are focused on identifying targets for adjuvant therapy, designing therapeutics, and testing them in animal models of HIV-1-mediated CNS disease. In general, these agents target one of two different HIV-1-mediated disease processes: neuroinflammation or neurotoxicity.

6.3. Immunomodulatory and neuroprotective agents

Several compounds targeted at reducing CNS immune activation and protecting neurons from toxic insults have been developed (Table 8). The rationale for using immunomodulatory agents as adjuvant therapy in neurocognitively impaired individuals is that reducing neuroinflammation should slow the entry of infected leukocytes into the brain, diminish alterations in BBB permeability, reduce production of neurotoxic mediators, maintain homeostatic functioning of astrocytes, and cumulatively, reduce neuronal injury and loss. The goal of using neuroprotective agents is to reduce the CNS neurotoxic burden and to provide opportunity for neuronal repair. The ultimate goal is that the use of immunomodulators and neuroprotective agents, as adjuvant therapy to antiretrovirals, will slow the progression of

Table 7. Antiretroviral therapy

Antiretroviral Agent	**CNS Penetration and Effective CSF Concentration** (569)	**Associated Toxicities** (568)
Nucleoside Reverse Transcriptase Inhibitors		
Zidovudine	high	bone marrow suppression: macrocytic anemia or neutropenia; GI intolerance; headache; insomnia; asthenia; lactic acidosis with rare hepatic steatosis
Abacavir	high	hypersensitivity reactions (can be fatal); fever, rash, nausea, vomiting, malaise, anorexia; sore throat, cough, shortness of breath
Stavudine	intermediate	peripheral neuropathy; lipodystrophy; hyperlipidemia; pancreatitis; rare rapidly progressive ascending neuromuscular weakness; lactic acidosis with hepatic steatosis
Lamivudine	intermediate	lactic acidosis with rare hepatic steatosis
Emtricitabine	intermediate	hyperpigmentation; lactic acidosis with rare hepatic steatosis
Tenofovir	low	asthenia; headache; diarrhea, nausea, vomiting; flatulence; renal insufficiency; lactic acidosis with rare hepatic steatosis
Didanosine	low	peripheral neuropathy; pancreatitis; nausea; lactic acidosis with rare hepatic steatosis
Non-Nucleoside Reverse Transcriptase Inhibitors		
Nevirapine	high	rash (including Stevens-Johnson syndrome); hepatitis; hepatic necrosis (can be fatal)
Efavirenz	intermediate	rash; dizziness, somnolence, insomnia, dysphoric dreams, confusion, abnormal thinking, impaired concentration, amnesia, agitation, depersonalization, hallucinations, euphoria; transaminase elevation; false-positive cannabinoid test
Delavirdine	low	rash; transaminase elevation; headaches
Protease Inhibitors		
boosted Aprenavir and Fosamprenavir	high	see below
boosted Atazanavir	high	see below
boosted Indinavir	high	see below
boosted Lopinavir	high	nausea, vomiting, diarrhea; asthenia; hyperlipidemia; elevated transaminases; hyperglycemia; fat maldistribution
unboosted Aprenavir and Fosamprenavir	intermediate	rash; diarrhea, nausea, vomiting; headache; hyperlipidemia; transaminase elevation; hyperglycemia; fat maldistribution;
unboosted Atazanavir	intermediate	indirect hyperbilirubinemia; prolonged PR interval; hyperglycemia; fat maldistribution; nephrolithiasis
unboosted Indinavir	intermediate	nephrolithiasis; nausea; indirect hyperbilirubinemia; hyperlipidemia; hyperglycemia; fat maldistribution; headache; asthenia; blurred vision; dizziness; rash; metallic taste; thromobocytopenia; alopecia; hemolytic anemia
Nelfinavir	low	diarrhea; hyperlipidemia; hyperglycemia; fat maldistribution; transaminase elevation
Ritonavir	low	nausea, vomiting, diarrhea; paresthesia; hyperlipidemia; hepatitis; asthenia; taste perversion; hyperglycemia; fat maldistribution
boosted/unboosted Saquinavir	low	nausea, diarrhea; headache; elevated transaminases; hyperlipidemia; hyperglycemia; fat maldistribution
boosted Tiprenavir	low	hepatotoxicity; rash (contains sulfa moiety); hyperlipidemia; hyperglycemia; fat maldistribution
Fusion Inhibitors		
Enfuvirtide	low	local injection site reactions; increased bacterial pneumonia; hypersensitivity reaction

neurodegeneration that is seen with HIV-1 infection. Several compounds have undergone placebo-controlled phase-I and phase-II clinical trials in individuals diagnosed with HAND. None of these agents has yet to be of clinical benefit.

6.4. Targeting leukocyte transmigration

Currently, there are no directed therapies available to treat HAND. Reverse transcriptase inhibitors, protease inhibitors, integrase inhibitors, fusion inhibitors, and CCR5 antagonists all target a specific stage in the lifecycle of HIV-1. As such, viral entry, replication, integration, assembly, and release can be reduced. Those agents with favorable BBB penetration can affect the viral load in the CNS. By reducing peripheral viral load, the percentage of HIV-1-infected monocytes transmigrating into the CNS can also be reduced and further attenuate CNS viral burden. Immunomodulators as adjuvant therapy to ART may also reduce neuroinflammation and neuronal injury. Attenuation of the CNS inflammatory cascade may reduce the toxic burden on neurons and glia and provide opportunity for recovery and repair. Neuroprotective agents may reduce the excitotoxic activity of neurons and glia and the general environment of oxidative stress that exists in the HIV-1-infected CNS. The leukocyte adhesion and transmigration cascade is a potential additional therapeutic target in the treatment of HIV-1 and prevention and modulation of CNS damage. This therapeutic strategy may provide for selectivity. By targeting specific adhesion molecules, enzymes, and signaling cascades that are specific to leukocyte-BBB interactions, certain leukocytes may be excluded from the CNS, while permitting their trafficking into other tissues. Leukocyte adhesion and transmigration across the CNS involves many different processes and requires a diverse repertoire of participating adhesion molecules, cytokines, chemokines, enzymes, and intracellular signals. As a result, the potential exists for a vast number of therapeutic targets. Much research is still required to define the specific mediators of monocyte and T-lymphocyte entry into the CNS. However some studies have already provided support for pursing leukocyte transmigration biology as a viable therapy for HIV-1 infection and HAND.

Integrins are an attractive candidate for directed therapy, as they are involved in leukocyte adhesion and arrest on the vasculature, formation of the transmigratory cup, homing to and migration through paracellular compartments, transcellular diapedesis, and signaling to tight junction and adherens junction complexes.

Table 8. Immunomodulatory and neuroprotective agents

Agent	Activity	Rationale for Use	Clinical Trial/Human Pilot Study Findings
Minocycline	tetracycline derivative	suppress T cell, macrophage, microglia activation (751-753) suppression of p38 MAPK-mediated NO production and neurotoxicity (754) associated with reduced: CCL2 CSF levels, monocyte and T-cell CNS recruitment, and axonal degeneration in SIV studies (755) attenuation of viral production and reactivation of latently infected cells in primary cultures of HIV- and SIV-infected macrophages, microglia, and lymphocytes (755, 756)	phase II clinical trial currently underway (ClinicalTrials.gov identifier:NCT00361257)
Peptide T **(d-ala-peptide-T-amide; DAPTA)**	synthetic octapeptide derived from a partial sequence of HIV-1 gp120 envelope protein with similarity to human vasoactive intestinal peptide	blocks binding of gp120 by interacting with CD4 and CCR5 *in vitro* (757-760) HIV-1 R5 strain-specific antiretroviral activity (757, 761) inhibits TNF-alpha production (762) neuronal protection upon exposure to gp120 or to HIV-1-infected monocytes/macrophages (761, 763)	phase II clinical trials: no statistically significant improvement in neuropsychiatric testing among HIV-1-impaired individuals as compared to placebo group, with trend toward improved cognition in individuals with greatest degree of baseline cognitive impairment (764) suppression of viral replication in circulating CD14+ monocytes and improved CD4 and CD8 T-cell titers (765)
Memantine	noncompetitive antagonist of the NMDA (N-methyl-D-aspartic acid) receptor (766)	neuroprotection against tat-, gp120-, and PAF-mediated neurotoxicity (687, 701, 767-770) currently approved for treatment of Alzheimer disease (771, 772)	phase II clinical trial: (773) no change in neuropsychological performance in individuals with HAD increased N-acetyl-aspartate (neuronal metabolite) levels on MRS indicating improved neuronal health
Nimodipine	L-type voltage sensitive calcium channel blocker (774)	neuroprotective against gp120 *in vitro* (767, 775)	phase I/II clinical trial: (776) no statistically significant change in neuro- psychological performance of individuals with HAD, although trend toward early improvement among individuals in high dose arm
Selegiline **(R-deprenyl)**	monoamine oxidase-B inhibitor (777)	inhibits ischemia-mediated neuron necrosis (778) up-regulates activity of the antioxidant enzymes superoxide dismutase and catalase (779, 780) neuroprotective through enhancement of neurotrophic factor synthesis (781-784) investigated for treatment of Alzheimer disease and Parkinson disease (785, 786)	phase II clinical trial: (787) no change in neuropsychological performance in individuals diagnosed with HAD
Sodium Valproate **(valproic acid, VPA)** **and Lithium**	inhibition of GSK-3beta which modulates synaptic plasticity in neurons through regulation of beta-catenin (788, 789)	protection from tat-, gp120- and PAF-mediated neurotoxicity and reversal of HIV-1-mediated damage to neuronal synapses (790-795)	10 week human pilot study: (796) low dose VPA: trend toward improved neuropsychiatric function 18 week human study: (797) high dose VPA: cognitive function deterioration 12 week human pilot study: (798) lithium: improved cognitive performance

Efalizumab and odulimomab are humanized monoclonal antibodies that target the $alpha_L$ integrin chain of LFA-1 ($alpha_L beta_2$; CD11a/CD18) and interfere with LFA-1/ICAM-1 interactions. As a result, leukocyte migration is attenuated. Efalizumab has shown success in the treatment of human psoriasis (596-598), while odulimomab has been effectively used in the treatment of graft-vs.-host disease, transplant rejection, renal ischemia-reperfusion injury, and atopic dermatitis in animal models (599-601). Despite its therapeutic benefit, Efalizumab was voluntarily withdrawn from the U.S. market by Genentech between April and June of 2009 because of an increased risk for the development of progressive multifocal leukoencephalopathy (PML) due to reactivation of latent JC virus in some individuals. Anti-CD18 monoclonal antibodies directed at the $beta_2$ chain of LFA-1 have failed to show clinical effect. Neither rovelizumab nor erlizumab had therapeutic benefit in phase II clinical trials of ischemia-reperfusion injury after myocardial infarction or stroke, causing them to be excluded from further testing (602, 603). In phase II clinical trials with enlimomab, a monoclonal antibody directed at ICAM-1, a negative effect was found in stroke patients (604). These results underscore the complex role of cell adhesion molecules in leukocyte recruitment during

different disease processes and the potential difficulties with using monoclonal antibodies as therapy (605).

Natalizumab is a monoclonal antibody directed against the $alpha_4$ integrin chain/CD49d of VLA-4 ($alpha_4beta_1$). By binding VLA-4, natalizumab interferes with VLA-4/VCAM-1 interactions and reduces the T_H1 inflammatory response which consists of interferon-gamma-secreting CD4 T-cells, CD8 effector T-cells, and activated monocytes/macrophages (606). Natalizumab has been successfully used in the treatment of active relapsing forms of multiple sclerosis (MS) (607-609) and Crohn's disease (610), but its use is also associated with the development of (PML) in some individuals (611-614). Thus in the context of MS, reducing the trafficking of destructive CD4 cells reduces the inflammatory burden in the CNS and destruction of the myelin sheath. However, impeding recruitment of CD8 cytotoxic lymphocytes may also impair cell-mediated immunity and control of virally-infected cells. Targeting integrins to reduce leukocyte trafficking into the CNS currently has both benefit and risk. It is hoped that future research will identify targets that can selectively impede entry of specific leukocyte subset populations into the CNS.

Chemokines control leukocyte trafficking by interacting with select receptors on specific leukocyte subsets. Thus, targeting specific chemokines and/or their receptors may disrupt leukocyte entry into the CNS. Monocytes characterized as $CCR2^{hi}/CX3CR1^{lo}$ have been identified as an inflammatory subset population, making CCR2 an attractive target for adjuvant therapy (615). CCR2 antagonists showed initial promise in preclinical models of autoimmune disease and human trials are ongoing (616). Similarly, T_H1 T-cells preferentially use CXCR3, CXCR6, and CCR5, while T_H2 T-cells express high levels of CCR4 and CCR8 (617-621). Such differences in chemokine receptor usage may provide an opportunity to target specific T-cell populations during transmigration. The risk to these therapies is that of effective immunosuppression in an already immunocompromised host and the potential for accelerating opportunistic infection and tumor-related pathology. However, targeting specific leukocytes and/or specific vascular beds based on proteomic profiling remains an attractive area of research.

Mutant chemokines may be an additional strategy for therapeutically targeting inflammation. Several chemokine derivatives have been shown to be effective at reducing leukocyte recruitment both *in vitro* and *in vivo*. A variant of CCL5 termed $^{44}AANA^{47}$-RANTES with abrogated glycosaminoglycan (GAG) binding properties (622) inhibits peritoneal recruitment of leukocytes in response to RANTES and thioglycollate (623, 624). In the MOG (myelin oligodendrocyte glycoprotein) EAE (experimental autoimmune encephalitis) murine model of MS, $^{44}AANA^{47}$-RANTES treatment resulted in delayed disease onset, reduced disease score, and reduction in axonal loss and demyelination area (625). This chemokine derivative does not form the oligomeric structures that are associated with RANTES chemotactic activity (626), enhancement of HIV-1 infection (627), and CCR5-mediated cellular apoptosis (628). $^{44}AANA^{47}$-RANTES was shown to dissociate RANTES oligomers into heterodimers, rendering the chemokine physiologically inactive (623). A CCL2 derivative called P8A-MCP-1 is an obligate monomer (629) which may be able to displace wild type CCL2 from endothelial GAGs (625). *In vivo*, P8A-MCP-1 reduces leukocyte recruitment in response to CCL2, prevents leukocyte adhesion to BMVEC, and attenuates disease symptoms in MOG-induced EAE (624, 630). This suggests that inhibiting chemokine binding to cellular or matrix GAGs may be a viable strategy for disrupting chemokine gradients and attenuating inflammation. Using either mutant chemokines with altered binding properties or small molecule inhibitors which displace chemokines from their GAG anchors or disrupt receptor binding may potentially reduce the chemotactic signals that drive leukocytes into the CNS. Specific targeting of CCL2, a chemokine that remains elevated in the CSF despite ART, may be of particular interest as adjuvant therapy in HIV-1 infection to treat and/or prevent neurological sequelae. However, the kinetics of blocking CCL2 may be critical to its efficacy in reducing neuroinflammation, as our laboratory showed that CCL2 inhibits tat-induced neuronal apoptosis when co-administered with tat (631).

Combinatorial therapy which targets several adhesion molecules and/or chemokine receptors on specific leukocyte populations and/or on specific vascular beds may selectively interfere with leukocyte transmigration into specific tissues. Agents designed to disrupt the formation of specific chemokine gradients at distinct anatomical sites may further provide selective inhibition of leukocyte entry into the CNS. A combinatorial approach to therapy that includes viral suppression, immunomodulation, neuroprotection, and selective interference of leukocyte transmigration may ultimately reduce the neurodegenerative pathology associated with HIV-1 infection.

7. SUMMARY AND PERSPECTIVE

Leukocyte transmigration into the CNS is a well coordinated, tightly regulated process. While much has been learned about the complex interplay of adhesion molecules, soluble factors, and junctional proteins on both the leukocyte and endothelium that regulate this process, a more complete understanding of these molecular mechanisms and the impact of HIV-1 infection on the process is necessary to develop more effective interventional strategies to limit the consequences of neuroinflammation and CNS HIV-1 infection.

The chronic HIV-1-mediated toxic and inflammatory insult on the CNS, combined with ART-associated toxicities, normal aging, and comorbid disease processes, are likely to substantially increase the prevalence of HIV-1-associated neurological impairment (632-634). Current ART treatments are ineffective at eliminating viral reservoirs and neuroinflammation. Thus, therapies targeted at reducing CNS inflammation, cellular activation, and neurodegeneration have the potential of reducing CNS

manifestations and improving the quality of life of individuals living with HIV-1.

Currently, no specific guidelines exist for treating HIV-1-associated CNS complications. An important question that will need to be answered is when to administer adjuvant therapy. HIV-1-mediated CNS damage begins early in the disease process. However, ART regimens are generally prescribed after CD4 T-cell titers reach a certain low level. It is unknown whether adjuvant therapy will show prophylactic benefit and be recommended for prescription at time of HIV-1 diagnosis. It is also unknown whether therapeutic adjuvants will improve cognition and the quality of life for those already experiencing HAND. It is difficult to predict what toxicities might develop in response to long-term treatment with adjuvants and what drug interactions might emerge. A comprehensive approach to treating HIV-1 infection that targets each component of the disease process may provide untold benefit.

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Abbreviations: CNS: central nervous system; BBB: blood brain barrier; HIV: human immunodeficiency virus-1; ART: antiretroviral therapy; BMVEC: brain microvascular endothelial cells; CSF: cerebrospinal fluid; PSGL-1; P-selectin glycoprotein ligand 1; NF-kappa B: nuclear factor kappa B; TNF-alpha: tumor necrosis factor alpha; CCL1: chemokine (C-C motif) ligand 1; VCAM: vascular cell adhesion molecule; VLA: very late antigen; MAPK: mitogen activated protein kinase; ICAM: intercellular adhesion molecule; LFA: leukocyte function antigen; ALCAM: activated leukocyte cell adhesion molecule; JAM: junctional adhesion molecule; PECAM: platelet endothelial cell adhesion molecule; LBRC: lateral border recycling compartment; PVR: polio virus receptor; DNAM: DNA accessory molecule; PrP^c: protease resistant protein-cellular isoform; MMP: matrix metalloproteinase; ZO: zonula occludens; VE-cadherin: vascular endothelial cadherin; VE-PTP: vascular endothelial protein tyrosine phosphatase; PMN: polymorphonuclear cells; HTLV: human T cell leukemia virus; gamma-GT: gamma-glutamyl transpeptidase; GLUT: glucose transporter; CCL2: chemokine (C-C motif) ligand 2; CCR2: chemokine (C-C motif) receptor 2; HIVE: HIV-1 encephalitis; SIV: simian immunodeficiency virus; PBMC: peripheral blood mononuclear cell; NO: nitric oxide; PKC: protein kinase C; TIMP: tissue inhibitor of metalloproteinase; CXCR3: chemokine (C-X-C motif) receptor 3; CCR5: chemokine (C-C motif) receptor 5; CXCR6: chemokine (C-X-C motif) receptor 6; CXCR4: chemokine (C-X-C) receptor 4; CCR8: chemokine (C-C motif) receptor 8; CCL4: chemokine (C-C) ligand 4; CCL5: chemokine (C-C) ligand 5; HAND: HIV-1- associated neurocognitive disorder; MTI-MMP: membrane type 1-matrix metalloproteinase; ADAM: a disintegrin and metalloprotease; MCP-1: monocyte chemoattractant protein 1; HAD: HIV-1-associated dementia; IRIS: immune reconstitution inflammatory syndrome; GAG: glycosaminoglycan; MOG: myelin oligodendrocyte glycoprotein; EAE: experimental autoimmune encephalitis; IL-1beta: interleukin-1beta; AF-6: ALL-1 gene fusion partner-6; PAR3: proteinase-activated receptor 3; PDZ: PSD-95/disc large/zonula occludens protein-1; sTNFR: soluble tumor necrosis factor alpha receptor; SNARE: soluble N-ethylmaleimide sensitive factor attachment protein receptor; Pyk2: proline-rich tyrosine kinase 2

Key Words: Blood-Brain Barrier, Transmigration, Paracellular Migration, Transcellular Migration, Diapedesis, Adhesion Molecules, Monocytes, Leukocytes, CCL2, HIV-1, NeuroAIDS, Therapeutics, Review

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