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Role of trophic factors on neuroimmunity in neurodegenerative infectious diseases

Dianne Langford[1] and Eliezer Masliah[1,2]

Departments of Pathology[1] and Neurosciences,[2] University of California, San Diego, La Jolla, California, USA

Viral infection of the central nervous system elicits a myriad of cellular, vascular, and neuroimmune factors that contribute to acute, subacute, and chronic damage to the brain. In response to cellular damage, the host is capable of producing trophic factors that may protect neuronal, glial, and endothelial cell populations. Both neurotrophic and angiotrophic factors can also operate by modulating the neuroimmune response, which plays a central role in the pathogenesis of the neurodegenerative process. In this regard, crosstalk signaling among host cells, components of the neuroimmune response, and virus could influence cell fate by production of trophic factors that protect or rescue neurons vulnerable to viral damage. In this context, the main objective of this review is to provide an overview of evidence in support of the role of trophic factors in regulating the neuroimmune response in chronic viral infections of the central nervous system. Special emphasis is placed on the interaction of the human immunodeficiency virus (HIV) Tat protein with endothelial, astroglial, microglial, and neuronal cells, resulting in altered expression of vascular endothelial growth factor, fibroblast growth factor, interleukin-8, and regulation of calcium flux via CXCR2, which directly influences neuronal cell fitness. *Journal of NeuroVirology* (2002) **8,** 625–638.

Keywords: blood-brain barrier; chemokine; CNS; cytokine; HIV-associated dementia; HIVE; IL-8; neurodegeneration

Introduction

During the process of viral infection of the central nervous system (CNS), numerous cellular, vascular, and neuroimmune factors contribute to acute, subacute, and chronic damage to the brain (Gendelman *et al*, 1997, 1998). Viral components can damage cells of the brain by both direct and indirect mechanisms. Cytolytic viruses directly infect neurons and/or glia leading to cell death (Robbins, 1999). Direct pathogenic effects include, for example, initiation of neuronal apoptosis by herpes simplex virus-1 (HSV-1), arbor virus, or rabies, usually resulting in acute damage to the CNS (Robbins, 1999). Infection of neural cells by noncytolytic viruses leads to production and activation of astrocytes and microglial cells. Activation of glial cells results in the production of immune factors such as cytokines and chemokines, which in turn might promote cell death. Collectively, the term neuroimmune response (NIR) is now used to refer to this cascade of events involving glial activation (Budka, 1991). Indirect damage by viral agents usually involves the NIR resulting in a protracted course of disease, as observed in human immunodeficiency virus (HIV) encephalitis (HIVE), cytomegalovirus encephalitis (CMVE), and Borna virus encephalitis (BVE). However, indirect damage mediated by the NIR may also contribute to the process of cell death in acute viral infection as observed in lymphocytic choriomeningitis virus (LCMV) (von Herrath and Oldstone, 1996).

The host-mediated NIR often results in damage to specific regions of the brain, to particular neural populations, and/or in leukoencephalopathy (Robbins,

Address correspondence to Dr. E Masliah, Department of Neurosciences, University of California, San Diego, La Jolla, CA 92093-0624, USA. E-mail: emasliah@ucsd.edu

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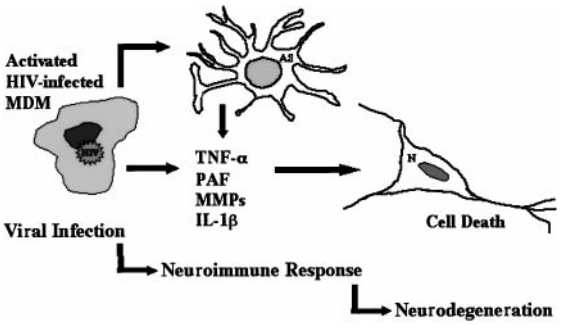

Figure 1 Virally induced NIR leading to neurodegeneration. Activated HIV-infected monocytes migrate across the BBB into the brain where they release cytokines and chemokines. Neuroimmune factors such as TNF-α, PAF, MMPs, and IL-1β in turn activate neighboring astrocytes, microglia, and neurons. Activation of the NIR leads to dendritic and synaptic damage and cell death via both autocrine and paracrine pathways. MDM, monocyte derived macrophage; AS, astrocyte; N, neuron; TNF-α, tumor necrosis factor-α; PAF, platelet-activating factor; MMPs, matrix metalloproteinases; IL-1β, interleukin-1β.

1999). For example, HSV-1 has a tropism for the limbic system of the brain but infects different neuronal populations within this region with equal efficiency (Caccamo and Garcia, 1993). On the other hand, JC virus (JCV) infection of oligodendrocytes, the cells that are responsible for myelin production, results in demyelination, which leads to progressive multifocal leukoencephalopathy (Robbins, 1999; Major *et al*, 1992). The NIR involves the production of numerous factors, such as cytokines and chemokines, by host cells in response to viral infection. Typically, macrophages, astrocytes, and microglia are primary effectors of this response (Poluektova *et al*, 2001). Cytokines and chemokines produced by virally infected cells induce both autocrine and paracrine cellular responses in the CNS. Thus, crosstalk with endothelial cells and pericytes of the blood-brain barrier (BBB) likely contributes to the NIR because these cells also produce neuroimmune factors. Accumulating evidence suggests an important role for cytokines and chemokines in both normal and pathogenic processes in the CNS, particularly in neurodegenerative disorders (Puma *et al*, 2001; Mrak *et al*, 1995; Horuk *et al*, 1997). Specific pathogenic characteristics of the virus, along with signaling events triggered by the NIR, contribute to the host's cellular response to viral infection of the CNS. Furthermore, the host's response to viral infection may be both deleterious and protective to cellular components of the CNS. In general, this response can be divided into three broad categories. First and most widely described is the virus-induced NIR that leads to neurodegeneration (Figure 1) (Maggirwar *et al*, 1999; Johnston *et al*, 2001; Nath *et al*, 1999). For example, in the brain, HIV predominantly infects cells of macrophage/microglial origin (Wiley *et al*, 1986). Infected cells become activated, producing cytokines and chemokines, leading to both excitotoxicty and the activation of neighboring cells (Xiong *et al*, 2000; Yeh *et al*, 2000). In point of fact, tumor necrosis factor-α (TNF-α) and platelet-activating factor (PAF) produced by activated microglia, not only amplify the inflammatory response but also cause considerable neurotoxicity (Persidsky *et al*, 2001) (Figure 1).

Secondly, viral exploitation of the host's immune system through molecular mimicry allows viral evasion of host-defense mechanisms (Figure 2) (Asensio

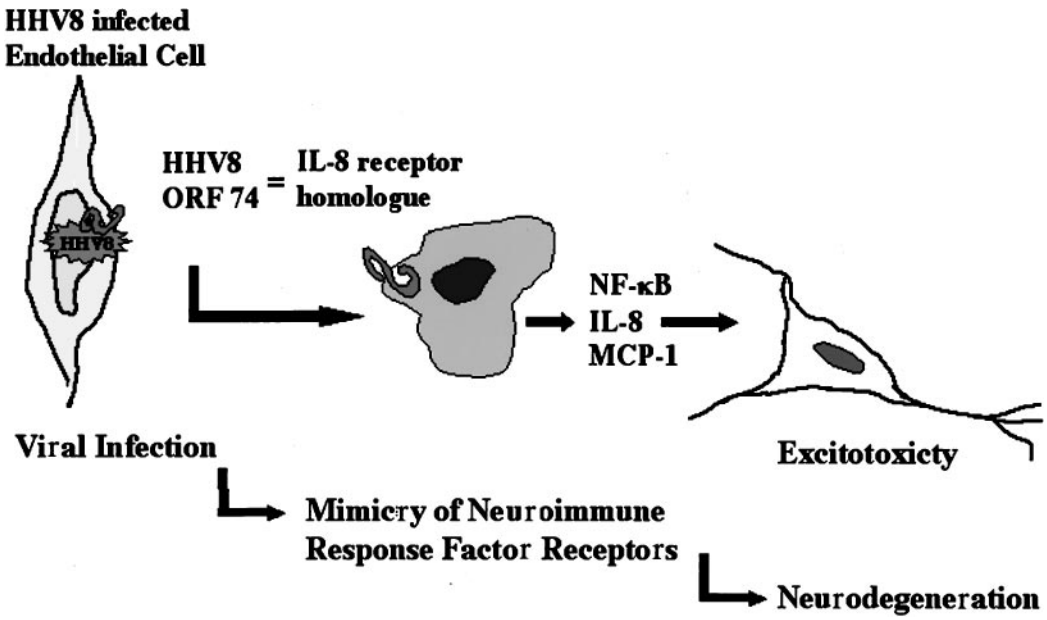

Figure 2 Viral exploitation of host's immune system by molecular mimicry. ORF 74 of HHV8 mimics the GCP receptor for IL-8 and activates NF-κB and AP-1, thereby inducing expression of a variety of NI factors leading to cell death. ORF, open reading frame; HHV8, human herpes virus 8; GCP, G-coupled protein; IL-8, interleukin-8; NF-κB, nuclear factor κB; AP-1, activator protein-1.

and Campbell, 1999; Arvanitakis *et al*, 1997; Murphy, 2001). In the case of mimicry, the virus mimics host cytokines, chemokines, and their receptors (for review see Murphy, 2001; Lalani and McFadden, 1999; Alcami and Koszinowski, 2000), leading to dysregulation of host-mediated immune responses. Numerous examples of viral mimicry exist and include homologues of cytokines and chemokines or their receptors and also factors with unique structures not related in primary amino acid sequence to neuroimmune factors (Murphy, 2001). Examples of molecular mimicry by HIV proteins include Tat that contains CXC and CC motifs and the exploitation of chemokines receptors by both gp120 and Tat to promote the NIR and viral infection of host immune cells (Murphy, 2001; Berger *et al*, 1999). Open reading frame-74 of human herpes virus 8 (HHV8) mimics the G-coupled interleukin-8 (IL-8) receptor, activates nuclear factor κB (NF-κB) and activator protein-1 (AP-1), and induces expression of interleukin-1 (IL-1), TNF, IL-8, monocyte chemoattractant protein-1 (MCP-1), basic fibroblast growth factor (bFGF or FGF2), and vascular endothelial growth factor (VEGF) (Arvanitakis *et al*, 1997; Murphy *et al*, 2000) (Figure 2). Poxviruses promote host-cell infection by encoding soluble versions of receptors for interferons (Smith *et al*, 1997, 1999). Viruses such as HIV, CMV, and vaccinia virus incorporate CD59 into the viral envelope, thereby protecting themselves from complement lysis (Alcami and Koszinowski, 2000).

Thirdly, and less well described, are the host-cell defense responses to both viral and neuroimmune components in an attempt to maintain cell fitness (Figure 3) (Ramirez *et al*, 2001; Nath *et al*, 1996; Benelli *et al*, 2000). Although cytokines and chemokines produced during the NIR cause cellular damage, the host's response includes production of trophic elements as well. Although considerable emphasis has been placed on understanding the mechanisms by which the NIR contributes to neurodegenerative disorders, less information is available on host responses that may counteract neuronal damage during viral infection. In this regard, crosstalk signaling among host cells and components of the NIR and virus could influence cell fate by production of trophic factors that protect or rescue neurons vulnerable to viral damage. In this context, the main objective of this review is to provide an overview of evidence supporting the role of trophic factors in regulating the NIR during chronic viral infections of the CNS. Special emphasis will be placed on the interaction of the HIV Tat protein with endothelial, astroglial, microglial, and neuronal cells, which results in altered expression of VEGF, FGF, and IL-8 and in regulation of calcium flux via CXCR2, which directly influences neuronal cell fitness.

NIR, trophic factors, and viral infection

Neural trophic factors can be produced by CNS cells in response to cell injury from viral infection and include, among others, neurotrophic and angiotrophic factors (Table 1). Neurotrophins such as nerve growth factor (NGF), brain-derived growth factor (BDNF), and neurotrophin 3 (NT3) are produced by neurons and glial cells to promote neuronal survival and

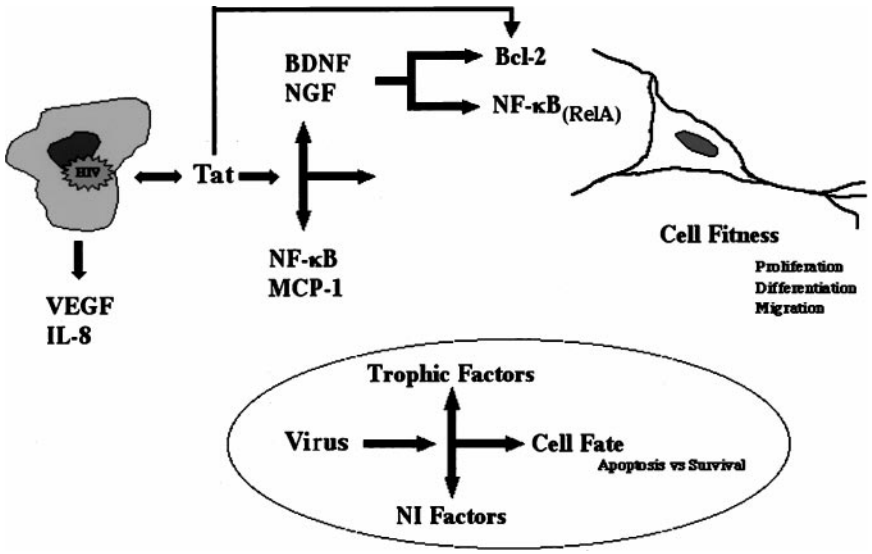

Figure 3 Host response to both viral and neuroimmune factors modulates cell fate. Crosstalk among host cells, viral proteins, and components of the NIR may influence cell fate by inducing trophic factor production. HIV Tat induces expression of VEGF, IL-8, NF-κB, and MCP-1. The RelA portion of NF-κB, along with the antiapoptotic Bcl-2, work with BDNF and NGF to promote neuronal cell fitness. Tat, transactivating transcription factor; VEGF, vascular endothelial growth factor; MCP-1, monocyte chemoattractant protein-1; BDNF, brain-derived neurotrophic factor; NGF, nerve growth factor.

Table 1 Trophic properties of growth factors

Growth factor	*Anglotrophic activity*	*Neurotrophic activity*	*Cell type maintained*
NGF	−	+++	Cholinergic neurons
BDNF	−	+++	Somatostatin-producing neurons
NT3	−	++	Hippocampal neurons
CDNF	+	++	Motor neurons
FGF1	+	++	Glutaminergic neurons
FGF2	+++	+	Endothelial cells (proliferation and migration)
IL-β	+++	++	Cholinergic neurons and endothelial cells
VEGF	++++	−	Endothelial cells (proliferation and migration)
Endothelin-1	++	−	Endothelial cells

growth (Encinas *et al*, 2000). Angiotrophic factors such as bFGF, VEGF, and endothelin are produced by astroglial and endothelial cells of the BBB and promote the survival, proliferation, and differentiation of brain microvascular cells (Sobue *et al*, 1999; Plate, 1999), to maintain BBB integrity. These factors may regulate or may be regulated by the NIR and will be discussed in more detail in following sections (Figure 3). Interactions among trophic growth factors, NIR components, and viral proteins contribute to cell fitness to influence cell fitness (Figure 4).

Neurotrophic factors play diverse roles during the progression of CNS infection by promoting increased viral replication or cooperating with viral and/or neuroimmune (NI) molecules to enhance neurotransmission. Trophic factors may also provide neuronal protection against toxic NI components, such as cytokines, chemokines, and harmful viral products (Table 1). For example, NGF and NT3 attenuate rabies infection (Castellanos *et al*, 2000) and can protect against HSV1 and HIV infection (Pakzaban and Chiocca, 1994). In contrast, NGF enhances the replication of Borna Virus Disease (BVD) and other viruses in glial cells (Carbone *et al*, 1993). In patients with viral meningitis, NGF (but not NT3) levels in cerebrospinal fluid (CSF) are elevated (Mizuno *et al*, 2000) and likewise in patients with HIVE, levels of bFGF and NGF are elevated (Boven *et al*, 1999), supporting the contention that viral infection promotes growth factor production not only by neurons, but also by cells of the NI system. Furthermore, in patients with HIVE, BDNF production by microglia is increased, suggesting that BDNF may affect neuronal survival and astroglial response via trkB receptors (Saarelainen *et al*, 2001). Interestingly, recent studies have also shown that gp120 cooperation with BDNF enhances somatostatin neurotransmission in HIVE, which otherwise is severely impaired in disease (Barnea *et al*, 1999). In addition, NGF and BDNF play important roles in neuronal survival in HIV infection by activating NF-κB, thereby inducing expression of the antiapoptotic Bcl-2 gene, which protects neurons

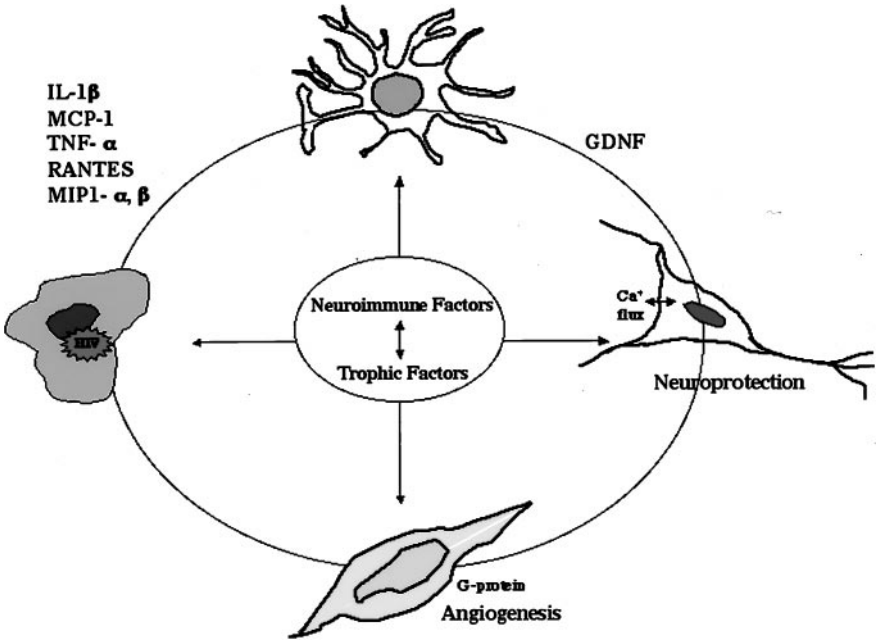

Figure 4 Interactions among neuroimmune components and trophic factors in neuroprotection and angiogenesis. IL-1β, interleukin-1β; MCP-1, monocyte chemoattractant protein-1; TNF-α, tumor necrosis factor-α; RANTES, regulated on activation normal T cell expressed and secreted; MIP-1α and -1β, macrophage inflammatory protein-1; GDNF, glial-derived neurotrophic factor; G-protein, G-coupled protein.

from the proapoptotic effects of HIV Tat (Ramirez *et al*, 2001) (Figure 3). Other neurotrophic factors under consideration include insulin-like growth factor (IGF) and hepatocyte growth factor (HGF); however, their potential role in regulating the NIR and HIV toxicity is unclear.

Though not well understood, these somewhat paradoxical roles of neural growth factors (both neurotrophic and angiotrophic) in response to viral infection of the CNS may provide insight into the complex interactions between host and pathogen (Figure 4). Moreover, understanding such signaling events is becoming a more attractive concept for chaperoning growth factor interactions in the treatment of neurodegenerative disorders. Considerable overlap exists between inflammatory factors and growth factors in the patterns of secondary gene regulation during biological responses to factors such as viral proteins. Convergence of signaling between TNF-α and Tat with VEGF at the mitogen activated protein kinase (MAPK) level (Figure 5) in the regulation of tissue factor expression (Mechtcheriakova *et al*, 2001) illustrates precisely such crosstalk interactions during biological responses. Taken together, accumulating evidence points to crosstalk between growth factors and components of the NIR in modulating complex cellular responses during viral infection of the CNS (Figure 4).

Viral infection then adds a third player into an already complex network of crosstalk between growth factors and NI components. Along with trophic and NI factors, viral proteins participate extensively in mediating the host's cellular response to infection. Consequently, in addition to growth factors, cytokines, and chemokines (Figures 3 and 4), we must also include viral proteins in our discussion of the role of trophic factors in the host's neuroimmune response (Figure 5) (Barillari *et al*, 1999) (Mechtcheriakova *et al*, 2001; Scheidegger *et al*, 2001; Liu *et al*, 2000). Although numerous examples exist, HIV provides an excellent model for describing these signaling interactions in the context of neuronal protection and maintenance of the BBB (Persidsky *et al*, 2000; Langford and Masliah, 2001). One striking example is the role of fractalkine in HIVE. Fractalkine is a neuronal chemokine with trophic activity that is elevated in HIVE patients (Pereira *et al*, 2001; Tong *et al*, 2000). Remarkably, this chemokine also regulates the NIR by modulating the activity and trafficking of macrophages into the CNS (Tong *et al*, 2000). Another example observed in HIV infection involves interactions among VEGF, bFGF, TNF-α, IL-1β, IL-8, and Tat in both neuronal and endothelial cell fitness (Figures 3 to 5) and is discussed extensively in later sections.

NI regulation, IL-8 and other trophic factors, HIV Tat

Interactions between NI factors and neurotrophic factors play an important role in the pathogenesis of HIVE (Figures 3 and 4). NI factors such as TNF-α, IL-1β, MCP-1, macrophage inflammatory protein 1

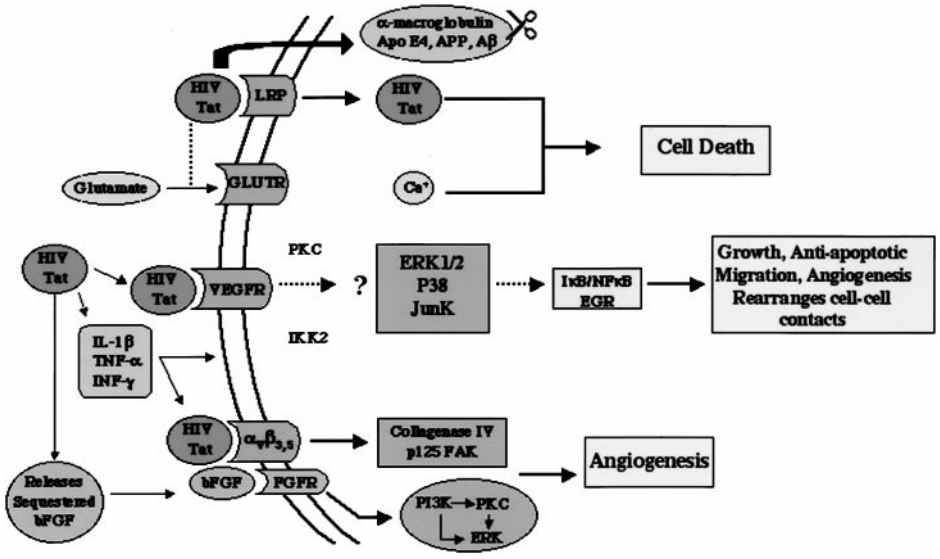

Figure 5 Convergence of signaling among Tat, host cells, and components of the NIR. Tat binds to LRP receptors, leading to cellular uptake of Tat and translocation to the nucleus. LRP binding by Tat also induces uptake and processing of α-macroglobulin, ApoE4, APP, and Aβ. Tat also interacts with glutamate/NMDA receptors, which, along with LRP signaling, can lead to calcium flux, neurodegeneration, and cell death. Synergy with bFGF promotes Tat binding to $\alpha_V\beta_{3,5}$ receptors to activate collagenase IV, p125FAK, and the PI3K/PKC/ERK pathways. Tat-mediated release of sequestered bFGF promotes this interaction. Binding of Tat to VEGF receptors induces the production of NI factors such as IL-1β, TNF-α, and IFN-γ. ApoE4, apolipoprotein E4; APP, amyloid precursor protein; Aβ, amyloid β; LRP, low-density lipoprotein receptor; NMDA, *N*-methyl-D-aspartate; PKC, phosphokinase C; IKK2, IκB kinase-2; $\alpha_V\beta_{3,5}$, integrin receptors.

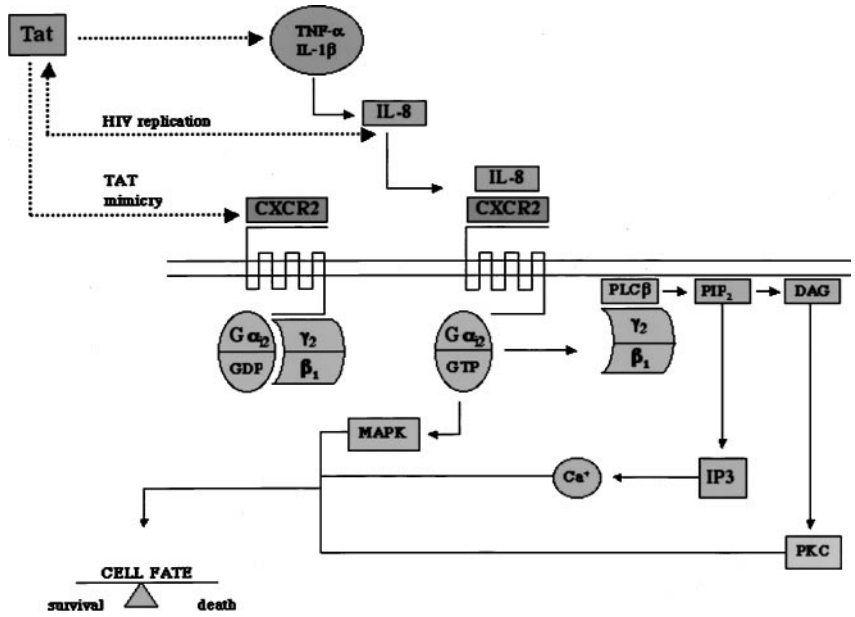

Figure 6 Convergence of HIV Tat and IL-8 signaling in determining cell fate. HIV Tat induces TNF-α and IL-1β production, leading to IL-8 expression and binding to CXCR2. Binding of IL-8 to CXCR2 initiates G-coupled protein signaling via GDP/GTP exchange and dissociation of $G\alpha_{i2}$ from $\gamma 2/\beta 1$ subunits. Dissociation leads to PLCβ and PIP2 stimulation. PIP2 then initiates the IP3 pathway, leading to calcium flux, DAG activation, and PKC signaling. IL-8 also promotes HIV replication, which in turn promotes release of Tat by HIV-infected cells. Tat mimics IL-8, thereby directly converging with IL-8 signaling to mediate cell fate. $G\alpha_{i2}$, G-α inhibitory protein; PLC-β, phospholipase C-β; PIP2, phosphoinositol phosphate-2; DAG, diacylglycerol; IP3, inositol triphosphate; PKC, phosphokinase C.

(MIP-1α and -1β), and regulated on activation normal T cell expressed and secreted (RANTES) produced by HIV-infected cells and by cells activated in response to HIV infection are capable of both directly damaging neurons or triggering a trophic response (Benveniste, 1994; Nottet, 1999) (Figure 3). For example, TNF-α and IL-1β augment the secretion of IL-8 by activated glial cells (Horuk *et al*, 1997). IL-8, a 10-kDa proinflammatory chemokine with trophic-like activity implicated in neuronal survival and regeneration (Araujo and Cotman, 1993; Limatola *et al*, 2000; Horuk *et al*, 1997; Xia *et al*, 1997; Murdoch and Finn, 2000) (Figure 6).

IL-8, also known as neutrophil-activating peptide 1, belongs to the family of CXC chemokines that include growth-related oncogenes α and β (GRO) and granulocyte chemotatic protein 2 (GCP-2), (Murdoch and Finn, 2000) (Figure 6) and stromal cell–derived factor-1 (SDF-1). T cells, neutrophils, fibroblasts, and endothelial and epithelial cells are stimulated by NF-κB to produce IL-8 (Shi *et al*, 2001; Choi *et al*, 2002; Lee *et al*, 2002). Moreover, IL-8 attracts T cells, neutrophils, basophils, and endothelial cells (Baggiolini *et al*, 1997). As one of the first chemokines described in the brain, IL-8 is produced by monocyte-derived macrophages, microglia, and astrocytes (Asensio and Campbell, 1999; Ehrlich *et al*, 1998; Hesselgesser and Horuk, 1999). IL-8 binds to CXCR1 and -2 receptors present on endothelial cells, astrocytes, and microglia and on cholinergic septal neurons and neurons of the hippocampus, cerebellum, and cortex (Belperio *et al*, 2000; Puma *et al*, 2001; Mahieux *et al*, 2001; Horuk *et al*, 1997; Meucci *et al*, 1998) (Figure 6). IL-8 has also been shown to function as a trophic factor in the maintenance of normal neuronal populations and promotion of neuron survival (Araujo and Cotman, 1993; Limatola *et al*, 2000; Horuk *et al*, 1997; Xia *et al*, 1997). For example, IL-8 enhances survival of rat hippocampal neurons through interactions with glial-derived neurotrophic factor (GDNF) (Araujo and Cotman, 1993). Furthermore, glial cell–derived IL-8 has been reported to modulate cholinergic septal neuron excitability by closing calcium channels via G-protein signaling (Puma *et al*, 2001). The ability of IL-8 to produce rapid calcium current reductions in neurons expressing CXCR1 and CXCR2 points to a trophic role for IL-8 in preventing excitotoxic neuronal death (Murdoch and Finn, 2000) (Figure 6). Moreover, the rat chemokine GRO-β, which is closely related to human IL-8 and shares the CXCR1 and -2 receptors, has an antiapoptotic effect on cultured cerebellar granular cells indirectly by mediating signaling of the non–*N*-methyl-D-aspartate (NMDA) alpha-amino-3-hydroxyl-5-methyl-4-isoxazolepropionic acid (AMPA) receptor (Limatola *et al*, 2000). In addition to its diverse roles in neuronal survival, IL-8 is also an important receptor-mediated stimulator of angiogenesis (Koch *et al*, 1992) and monocyte adherence (Gerszten *et al*, 1999) (Baggiolini *et al*, 1994).

IL-8 interactions with HIV promote viral replication

HIV Tat stimulates the production of IL-8 and GRO-α by T cells and macrophages (Lane *et al*, 2001a, 2001b) (Figures 5 and 6) and as a result, in HIV patients, levels of IL-8 are elevated both *in vivo* in the sera and *in vitro* in HIV-infected cells (Denis and Ghadirian, 1994; Matsumoto *et al*, 1993; Mori *et al*, 1995, 1998). In turn, IL-8 and GRO-α then stimulate HIV-1 replication (Lane *et al*, 2001b). GRO-α is also a CXC chemokine with 43% amino acid identity to IL-8 and ligates CXCR2 (Baggiolini *et al*, 1994). Interestingly, unlike CXCR4, neither CXCR1 nor CXCR2 function as coreceptors for HIV-1 (D'Souza *et al*, 2000). Striking similarities between the cell signaling activities of HIV Tat (Figure 5) and IL-8 (Figure 6) may provide clues as to how host/pathogen components interact to mediate neuronal cell fate in HIV infection (Figure 5). For example, IL-8 prevents cell death via regulation of glutamate receptors that are implicated in the neurotoxic effects of Tat and, effects of Tat (Figure 6). The HIV Tat protein potentiates NMDA-mediated neurotoxicity by increasing intracellular calcium release and uptake of extracellular calcium uptake in rat hippocampal neurons and in rat cortical neurons via the G-protein pathway (Nath *et al*, 1996; Haughey *et al*, 2001; Perez *et al*, 2001) (Figure 6). It is possible that IL-8 protects against Tat toxicity by reducing intracellular calcium.

Another example of growth factor neuroprotection against NMDA-mediated excitotoxic neurodegeneration is that GDNF and neublastin (NBN) (also known as artemin) protect hippocampal neurons against excitotoxic damage (Bonde *et al*, 2000). Members of the GDNF family of neurotrophins support survival of dopaminergic neurons in the substantia nigra and spinal and facial motor neurons (Hamilton *et al*, 2001; Saarma and Sariola, 1999). Like VEGF, bFGF, and HIV Tat, GDNFs bind to heparin sulfate proteoglycans found both in the extracellular matrix and on the cell surface. Hamilton *et al* (2001) point to the significance of heparin receptor binding in relation to the use of growth factors to enhance dopaminergic metabolism in neurodegenerative diseases by emphasizing the complex network of cross-talk among growth factors, NI components, and viral proteins on neurodegeneration.

Although Kaposi sarcoma (KS) is rarely reported to affect the brain microvasculature, signaling interactions occurring during HIV-related KS provide a noteworthy example of viral protein manipulation of host immune response and growth factor–mediated defense strategies. HIV Tat mimics the effect of VEGF on endothelial cells via PAF-1 synthesis, activates the angiogenic process by binding to integrin receptors, and acts with bFGF to promote endothelial cell growth and angiogenesis (Scheidegger *et al*, 2001; Del Sorbo *et al*, 2001; Albini *et al*, 1996; Barillari *et al*, 1999) (Figure 5). Moreover, in recent reports, IL-8 has been presented as a key player in crosstalk between the HIV Tat protein and modulation of angiotrophic factors such as bFGF, VEGF, and endothelin-1 (Koch *et al*, 1992; Gershengorn *et al*, 1998) (Figures 5 and 6). Interestingly, endothelin-1, a cytokine that plays a role in vasodilation, vasoconstriction, and cell proliferation, is elevated in the spinal fluid of patients with HIVE and may contribute to its pathogenesis (Rolinski *et al*, 1999; Zidovetzki *et al*, 1999). Furthermore, the G-protein–coupled receptor of KS herpes virus (KSHV, also known as HHV-8) has striking sequence and structural similarity to IL-8 receptors CXCR1 and -2 (Cesarman *et al*, 1996; Guo *et al*, 1997). KSHV induces NF-κB that in turn stimulates IL-8 secretion (Shepard *et al*, 2001). In this regard, IL-8 and several CXC chemokines containing the N-terminal Glu-Leu-Arg (ELR) sequence function as angiogenic factors (Koch *et al*, 1992; Belperio *et al*, 2000).

In summary, the role of IL-8 during HIV infection of the brain is complex and involves the induction of angiogenic factors (Figure 5) with which Tat synergizes or directly mimics (Figure 6). IL-8 also functions as an autocrine factor, is induced by Tat, and promotes HIV replication via stimulation of the CXCR2 receptor to influence G-coupled calcium channel regulation (Figure 6). Communication among angiotrophic and neurotrophic factors, IL-8, and Tat in neural fitness during HIV infection of the CNS is complex and the majority of data support interactions among these components in determining cell fate.

Role of FGF1 and -2 in HIVE

As described in the previous section, trophic factors play an important role in the pathogenesis of viral encephalitis by regulating the NI response, protecting the neurons against toxins, and modulating viral replication. In addition, more recent studies have shown that trophic factors interact with viral proteins and chemokines in regulating the permeability of the BBB and in the process of angiogenesis in response to CNS damage (Arese *et al*, 2001; Persidsky *et al*, 2001; Salcedo *et al*, 1999). Among the trophic factors involved in viral encephalitis, special attention has been placed on the role of FGF in the progression of these disorders. The FGF family includes more than 10 members of heparin-binding proteins (Klint and Claesson-Welsh, 1999). Of interest in the brain are FGF1 (acidic, aFGF), which is produced by neurons (Figure 7**A–D**) and is primarily neurotrophic (Figure 7**E–H**), and FGF2 (basic, bFGF), which is produced by glial cells (Figure 8**A–D**) and is angiotrophic (Walicke and Baird, 1988; Eckenstein, 1994; Klint and Claesson-Welsh, 1999) (Figure 8**E–H**).

Fibroblast growth factors maintain a broad range of neurons, including those selectively vulnerable to virally derived factors (Abe and Saito, 2001;

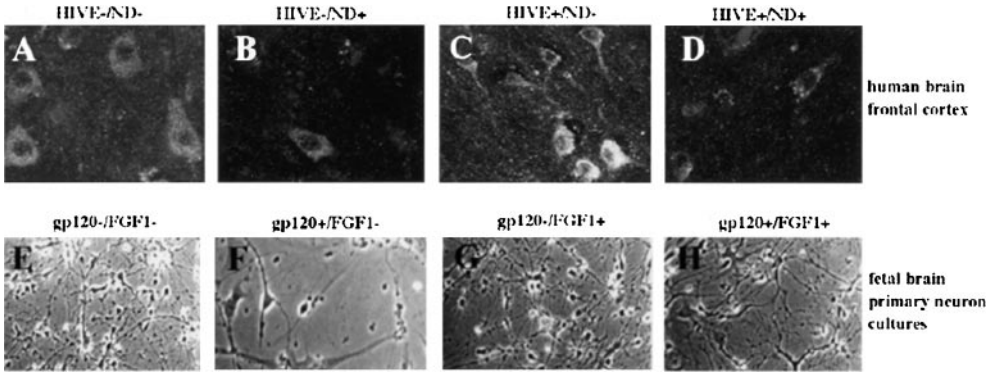

Figure 7 FGF1 protects neuronal cells against HIV-mediated toxicity. Panels **A–D**: Sections from human frontal cortex were immunostained with an antibody against FGF1 and analyzed with a laser scanning electron microscope. Panels **E–H**: Human fetal neurons were treated with or without FGF1 and gp120 and analyzed with a phase contrast microscope. **A**: In patients without HIVE or neurodegeneration, there were low levels of FGF1 expression. **B**: In patients without HIVE but with neurodegeneration, neuronal FGF1 expression levels were reduced. **C**: In patients with HIVE but no neurodegeneration, FGF1 expression levels were elevated. **D**: In patients with HIVE and neurodegeneration, levels of FGF1 were reduced. **E**: Normal appearance of human cortical neurons under basal conditions. **F**: Treatment with gp120 (25 nM, 6 days) resulted in cell damage. **G**: Treatment with FGF1 (20 nM, 24 h) promoted neurite outgrowth. **H**: Pretreatment with FGF1 prevented gp120-mediated toxicity.

Everall *et al*, 2001; Thorns and Masliah, 1999). Furthermore, they sustain the integrity of the BBB and levels are altered in patients with HIVE (Boven *et al*, 1999; Everall *et al*, 2001). Consequently, their potential value in the treatment of neurological disorders is under intense consideration. This is important for patients with AIDS because neurocognitive alterations in this population continue to be a significant problem (Grant *et al*, 1995; Dore *et al*, 1999; Starace *et al*, 1998; McArthur *et al*, 1993). However, to date there are no therapeutic strategies targeted at protecting the CNS and preventing neuronal damage and death due to HIV infection. During HIV infection, pathologically, the brain is affected by a spectrum of inflammatory changes (Budka *et al*, 1991; Tyor *et al*, 1992), dendritic and synaptic damage (Masliah *et al*, 1997; Everall *et al*, 1999), and neuronal loss (Everall *et al*, 1993). Increasing viral load in the CNS is associated with worsening neuronal damage, and correlates with the early onset of cognitive impairment (Masliah *et al*, 1997; Everall *et al*, 1999). However, the relationship among cognitive impairment, HIVE, and neurodegeneration is complex because not all patients with HIVE show cognitive impairment and neurodegeneration (ND) (Wiley and Achim, 1994). This phenomenon might indicate that the latter group of individuals (HIVE+/ND−) has the capacity to produce neurotrophic factors able to protect neurons against the deleterious effects of HIV. Supporting this possibility, recent studies have shown that levels

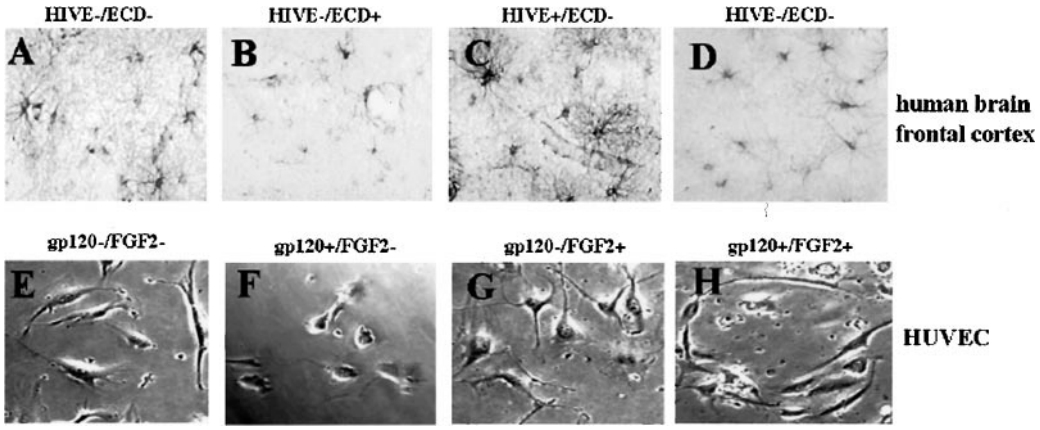

Figure 8 FGF2 protects microvasculature against HIV-mediated toxicity. Panels **A–D**: Sections from human frontal cortex were immunostained with an antibody against FGF2 and analyzed by bright field microscopy. Panels **E–H**: HUVECs were treated with or without FGF2 and gp120 and analyzed with a phase contrast microscope. **A**: In patients without HIVE or endothelial cell damage, there were low levels of FGF2 expression. **B**: In patients without HIVE but with endothelial cell damage, FGF2 expression levels were reduced. **C**: In patients with HIVE but without endothelial cell damage, FGF2 levels were elevated. **D**: In patients with HIVE and endothelial cell damage, levels of FGF2 were reduced. **E**: Normal appearance HUVECs under basal conditions. **F**: Treatment with gp120 (25 nM, 24 h) resulted in cell damage. **G**: Treatment with FGF2 (20 nM, 24 h) promoted HUVEC proliferation. **H**: Pretreatment with FGF2 prevented gp120-mediated toxicity. HUVECs, human umbilical vein endothelial cells; ECD, endothelial cell damage.

of FGF are increased in HIVE patients with preserved neuronal architecture and that this trophic factor protects primary cultured neurons from the neurotoxic effects of HIV gp120 (Everall *et al*, 2001) (Figure 7). Moreover, in patients with KS, high levels of FGF2 (Faris *et al*, 1998) produced by the tumor are associated with a decreased risk for neuronal degeneration and neurological impairment (Liestael *et al*, 1998). In contrast, neurodegeneration in patients with HIV is associated with low levels of FGF1 expression (Everall *et al*, 2001) (Figure 7). Although mechanisms by which FGF1 might be neuroprotective against HIV are not completely clear, several possibilities have been proposed. There may be antagonism of excitatory amino acid toxicity (Inklestein *et al*, 1993) by regulating expression of glutamate receptors because it is postulated that gp120 interacts with NMDA/glutamate receptors (Dreyer *et al*, 1990). On the other hand, it has recently been shown that FGF down-modulates cell surface expression of CXCR4 receptors, which are coreceptors for HIV cellular entry (Sanders *et al*, 2000). Furthermore, CXCR4 expression by neurons appears to be an important mediator of gp120 neurotoxicity (Kaul and Lipton, 1999), providing another example of a trophic factor that interacts with the NIR during the progression of viral encephalitis. Alternatively, the signaling pathway downstream from FGFR1 may mediate neuroprotective effects of FGF1 (Hashimoto *et al*, 2002). In this regard, FGF1 binds to FGFR1, leading to dimerization of the receptor, with phosphorylation and activation of tyrosine kinase (Klint *et al*, 1999). There is an array of signal transduction molecules activated by the FGFR1 dimer, including phospholipase C-γ (PLC-γ), the Src family kinase, Src homology phosphatase type-2 (SHP-2), focal adhesion kinase (FAK), phosphatidylinositol 3′ kinase (PI3 kinase), FGF receptor substrate 2 (FRS2), which is a recently characterized 90-kDa adaptor molecule, and Grb-2, which activates Ras (Klint and Claesson-Welsh, 1999; Williams and Doherty, 1999). FGF induces sustained activation of MAP kinases ERK1 and -2, which are downstream of Ras in the pathway (Klint *et al*, 1999). MAP kinase activation may be important in mediating a number of neurotrophic effects, although independent pathways may also be activated (Renaud *et al*, 1996). Furthermore, FGF binding activates both the p90 (rsk) and the PI3K/AKT pathways, which in turn stabilize membrane-associated β-catenin (Maggirwar *et al*, 1999). Degradation of β-catenin is promoted by glycogen synthase kinase-3β (GSK3β) and FGF inhibits endogenous GSK3β, possibly by p90 (rsk) (Torres *et al*, 1999) or the PI3K/Akt signaling cascade. Although activation of GSK3β might lead to cell death, inhibition of this enzyme is associated with cellular survival (Pap and Cooper, 1998). Therefore, FGF1 might be neuroprotective via regulation of GSK3β pathway (Hashimoto *et al*, 2002) (Figure 9**A**). Further supporting a role of this pathway in HIVE, a recent study showed that FGF1 alters GSK3β activity and that in

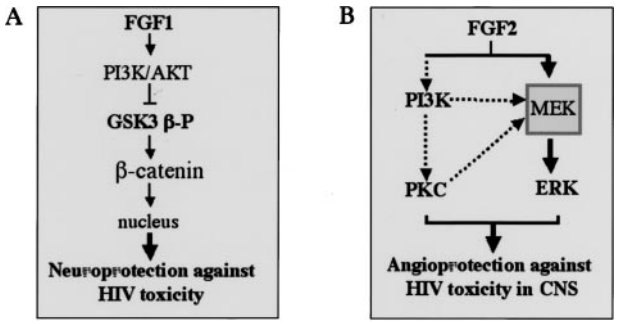

Figure 9 (**A**) FGF1 binding to FGFR activates the PI3K/AKT pathway in neuronal cells. Activation of AKT leads to phosphorylation and inactivation of GSK3β. GSK3β inactivation allows β-catenin translocation into the nucleus, thereby promoting cell survival. FGF1 treatment protects neurons from gp120-mediated toxicity. (**B**) FGF2 binding to FGFR activates PI3K/MAPK signaling in HUVECs. PI3K stimulation results in both PKC-dependent and -independent MAPK activation and ERK phosphorylation. FGF2 treatment protects HUVEC from gp120-mediated toxicity.

HIV-infected cells the transactivator molecule Tat is capable of inducing GSK3β (Maggirwar *et al*, 1999). In summary, FGF1 might be neuroprotective against HIV via regulation of intracellular signaling pathways important for cell survival (Figure 9**A**).

Another aspect through which FGF may regulate progression of viral encephalitis and the NIR is in maintaining BBB integrity, which is critical to prevent the passage of potentially harmful factors, such as pathogens or toxins, into the brain (Langford and Masliah, 2001). During the progression of CNS infectious disease, pathogens might gain access to the brain by compromising the integrity of BBB (Achim *et al*, 1993; Langford and Masliah, 2001; Persidsky *et al*, 2000). In the course of AIDS, HIV is proposed to enter the brain at early stages, disrupting the components of the BBB, resulting in a chronic state of inflammation known as HIV encephalitis (Zink *et al*, 1999). HIVE is characterized by the presence of HIV in the brain, the formation of multinucleated giant cells and microglial nodules, astrogliosis, and myelin pallor (Budka, 1991), the combined effects of which could result in cognitive impairment (Wiley *et al*, 1999; Wiley and Achim, 1994). Endothelial cells of the BBB are the first point of contact between viral products and are the front line of defense against viral entry into the CNS. Alterations in signaling between components of the BBB with either HIV proteins or factors produced in response to HIV infection, such as cytokines and chemokines, disrupt BBB integrity and result in compromise, thereby promoting transmigration of activated monocytes or HIV-infected cells into the brain (Persidsky *et al*, 2000). Toxic products released from HIV-infected cells, such as gp120, Tat, or Nef, together with cytokines and chemokines from activated monocytes, can act to increase BBB permeability (Sporer *et al*, 2000; Park *et al*, 2001; Weiss *et al*, 1999; Woodman *et al*, 1999). For example, gp120

has been shown to promote apoptosis of human umbilical vein endothelial cells (HUVECs) (Huang *et al*, 2001; Ullrich *et al*, 2000) (Figure 8) and to alter the BBB in transgenic mice (Toneatto *et al*, 1999), whereas other factors, such as growth factors, may work to preserve BBB integrity. In this context, FGF2 is of particular interest for several reasons. FGF2 is produced by astrocytes that are in close proximity to endothelial cells of the BBB (Figure 8) and among the known astrocyte-derived growth factors, and FGF2 is the only one that represents the signaling actions of astrocytes to the BBB (Klint *et al*, 1999; Sobue *et al*, 1999). Of the four FGF receptors, FGFR1 is mainly expressed on neurons and endothelial cells, whereas FGFR2 and FGFR3 are found on glial cells (Chambers *et al*, 2000; Clarke *et al*, 1993; Dodart *et al*, 2000; Eckenstein, 1994; Klint and Claesson-Welsh, 1999). FGF2, which binds to FGFR1, has been shown to exhibit a wide range of angiotrophic effects (Klint *et al*, 1999; Sobue *et al*, 1999) and promotes the survival of cortical and hippocampal neurons (Morrison *et al*, 1986; Sendtner *et al*, 1991; Walicke and Baird, 1988). During the progress transmigration of HIV macrophages across the BBB, activated cells secrete cytokines and chemokines which interact with astroglial cells of the BBB to promote FGF2 production (Langford and Masliah, 2001). Possible candidate cytokines and chemokines include IL-1β and TNF-α, bringing full circle the crosstalk among virus, NIR, and trophic factors. It has been shown that cytokines act on specific astroglial cell surface receptors, triggering a cascade of signaling events that have not yet been completely characterized. An example of such events is the production of the transcription factor early growth response-1 (EGR-1), which binds to the promoter of FGF2 to induce its expression (Mechtcheriakova *et al*, 2001). Potential effects of the FGF2 might range from maintenance of the BBB to regeneration of endothelial cells (Figure 8) and neurons. Characteristics of these effects might depend on the stage of the disease. For example, in early stages FGF2 production might increase BBB permeability and facilitate trafficking, whereas in later stages it might promote repair of the compromised BBB. In this scenario, interactions between NIR and trophic factors might have paradoxical effects, depending on disease progression and severity. Similar to FGF1, the mechanisms by which FGF2 might exert these effects are under intense investigation. Among them, regulation of transduction events via the ERK signaling (Figure 9**B**) might be important in the early stages, whereas at later stages regulation of the expression of CXCR4 and other receptors relevant to the process of angiogenesis and vascular repair might be favored.

In conclusion, a common theme begins to emerge in which chemokines, growth factors, and viral proteins convergence to modulate host response to neurodegenerative infectious diseases. There is increasing evidence that supports a role for neuroregulatory interactions of trophic factors and the NIR during viral infection, providing a potential target for the development of new therapeutic approaches.

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