Dual role of inflammation in CNS disease

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ABSTRACT Inflammatory responses in the CNS have usually been perceived to cause or contribute to neuron injury. However, emerging evidence suggests that inflammatory reactions can also be neuroprotective. The nervous and immune systems employ overlapping mechanisms and shared mediators that promote cross-talk between the two systems. Immune cells, for example, produce not only neurodestructive molecules but also factors that can support neuroaxonal growth, survival, and plasticity. This might explain why inflammatory reactions may contribute to both injury and protection of neurons. The dual role of CNS inflammation also has important therapeutic implications that are only beginning to be explored. **NEUROLOGY 2007;68 (Suppl 3):S58–S63**

Inflammation in the CNS is usually considered to have deleterious, neurotoxic effects, but a growing body of evidence suggests that inflammatory reactions may also be beneficial.[1-7] A possible molecular explanation for these findings is that the nervous and immune systems engage in intense cross-talk.[8] Both systems produce a range of factors (e.g., cytokines for the immune system and neurotrophic factors for the CNS) that modulate cell growth and differentiation.

Interestingly, the factors expressed by immune and CNS cells overlap. Neither cytokines nor neurotrophic factors are completely exclusive to either system.[8] For example, B-cell-activating factor (BAFF) is a member of the tumor necrosis factor (TNF) family required for peripheral B-cell survival and homeostasis.[9] It was long believed that immune cells such as monocytes, macrophages, and neutrophils were the only source of BAFF. However, Krumbholz et al.[10] found that BAFF is also expressed in the normal human brain, and its production by reactive astrocytes might foster B-cell survival in multiple sclerosis (figure 1). Conversely, brain-derived neurotrophic factor (BDNF), a member of the nerve growth factor (NGF) neurotrophin family, has been viewed predominantly as an essential regulator of the survival and differentiation of various neuron populations during development and after injury. However, BDNF is produced not only by neurons but also by activated human T cells, B cells, and monocytes (see figure 1). Specifically, the inflammatory cells that accumulate in degenerative and autoimmune nervous system lesions also secrete BDNF.[12,13] These shared neuroimmune mediators enable the immune and nervous systems to engage in cross-talk, and they offer a rationale for the dual role of inflammatory reactions in the CNS.

This brief overview examines the contribution of inflammation to MS pathogenesis. We describe immune cell-derived neurotrophic factors and assess the functional neuroprotective effects of immune cells, focusing on T lymphocytes. Finally, we look at the evidence supporting the possible neuroprotective potential of currently used immunomodulatory agents. We argue that inflammation in CNS disease is, in essence, an ambivalent process that may have both protective and destructive effects. The net effect of inflammation in any particular pathologic situation will be determined by whether one process outweighs the other (figure 2).

NEUROTROPHIC FACTORS

Neurotrophic factors comprise a family of proteins essential for the development of the CNS in vertebrates. Neurotrophic action is pleiotropic. In addition to mediating neuron survival, neurotrophic factors regulate a host of neuronal and glial cell activities, including growth of axons and dendrites, synaptic structure and plas-

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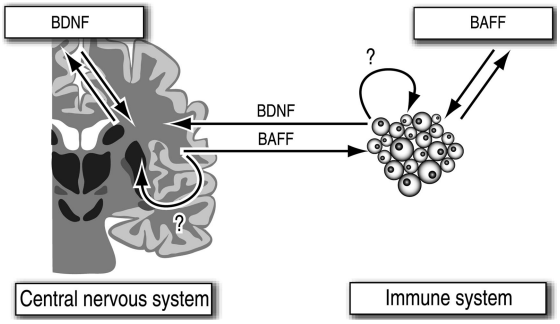
BDNF is produced and acts in the CNS, but was shown also to be produced by various immune cells that can "import" BDNF into the CNS to support neuron survival. Conversely, BAFF is produced and acts in the immune system, but was recently shown also to be locally produced by CNS cells (astrocytes), which can support the long-term survival of B cells in the CNS of patients with MS. BAFF, B-cell-activating factor; BDNF, brain-derived neurotrophic factor (reviewed in Kerschensteiner et al.[8] and Meinl et al.[11]).

Figure 1 Two examples of cross-talk between the immune and central nervous systems



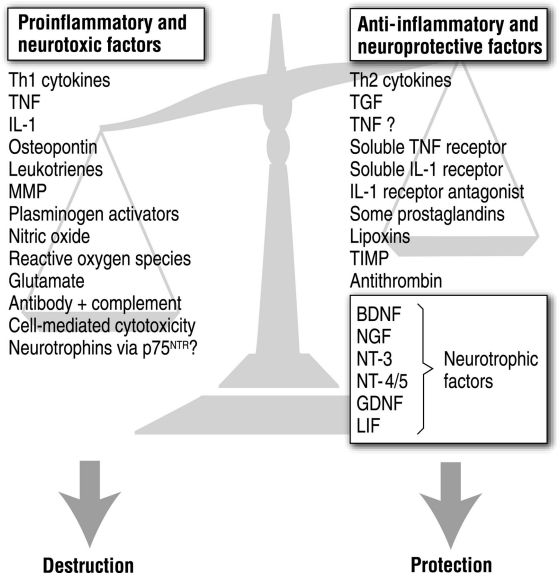
ticity, neurotransmitter expression, and long-term potentiation.[14-16] Furthermore, many neurotrophic factors profoundly influence various immune cell functions, such as migration, activation, differentiation, and local antigen presentation.[17-20]

Three families of neurotrophic factors have been characterized. They include the following: (a) NGF-related neurotrophic factors, the neurotrophins: NGF, BDNF, neurotrophin-3 (NT-3), and neurotrophin-4/5 (NT-4/5); (b) glial cell line-derived neurotrophic factor (GDNF) family ligands: GDNF, neurturin, artemin, and persephin[21,22]; (c) the neuropoietic cytokines, such as ciliary neurotrophic factor and leukemia inhibitory factor[23]; and (d) miscellaneous other factors that also exert neurotrophic effects.

BDNF. BDNF is a member of the NGF-related neurotrophin family. It plays an essential regulatory role in neuron plasticity and survival and in neurotransmitter release and dendrite growth.[14,16] Moreover, BDNF can prevent neuroaxonal damage in animal models after a variety of pathologic insults and injuries.[15] These actions affect key cell populations, including sensory, cerebellar, and spinal neurons. BDNF binds preferentially to TrkB receptor (gp145trkB), which is expressed on neuronal cells. Like other neurotrophins, BDNF also binds to the p75 neurotrophin receptor (figure 3).

Although neurons were considered to be the main cellular source of BDNF, work from our group and others demonstrated that various immune cells secrete BDNF in vitro.[12,25-27] Specifically, BDNF expression is increased after antigen stimulation in T-helper (Th)1 and Th2 $CD4^+$ cell lines specific for myelin autoantigens such as myelin basic protein (MBP) and myelin oligodendrocyte glycoprotein.[6,12] The neurotrophin was bioactive, as it supported neuron survival in vitro. Moreover, inflammatory cells in brain lesions and perivascular locations in patients with acute disseminated encephalitis and MS also expressed BDNF.[4,12] Notably, lesion areas with high numbers of demyelinating macrophages exhibited enhanced BDNF immunoreactivity.

Figure 2 The dual role of inflammation



BDNF, brain-derived neurotrophic factor; GDNF, glial cell line-derived neurotrophic factor; IL-1, interleukin 1; LIF, leukocyte inhibitory factor; MMP, matrix metalloproteinase; NGF, nerve growth factor; NT, neurotrophin; $p75^{NTR}$, p75 neurotrophin receptor; TGF, transforming growth factor; Th, T-helper cell; TIMP, tissue inhibitor metalloproteinase; TNF, tumor necrosis factor. Adapted from Kerschensteiner et al.,[8] with permission.

Subsequently, Stadelmann et al. found that the BDNF receptor gp145trkB is also found in neurons adjacent to MS lesions and in reactive astrocytes within the plaques.[4] These observations indicate that, in certain situations, immune infiltrates common to "neuroinflammatory" diseases (such as MS) and "neurodegenerative" diseases (such as Alzheimer disease) import BDNF and other neuroprotective neurotrophic mediators to the CNS. These findings may explain why the healthy immune system contains large numbers of autoreactive T lymphocytes (see below). However, neurotrophin signaling may engage other pathways, producing a more complex response. Precursor proteins, known as proneurotrophins, are cleaved proteolytically to produce mature BDNF, NGF, NT3, and NT4. Although mature neurotrophins bind with high affinity to cognate Trk receptors to foster neuronal cell survival, proneurotrophins bind preferentially to the p75 neurotrophin receptor to promote cell death (figure 3). The predisposition to produce both proapoptotic and antiapoptotic responses has been described as the "yin and yang" of neurotrophin action.[28] In this conceptual model, the particular effect depends on the form of the activated neurotro-

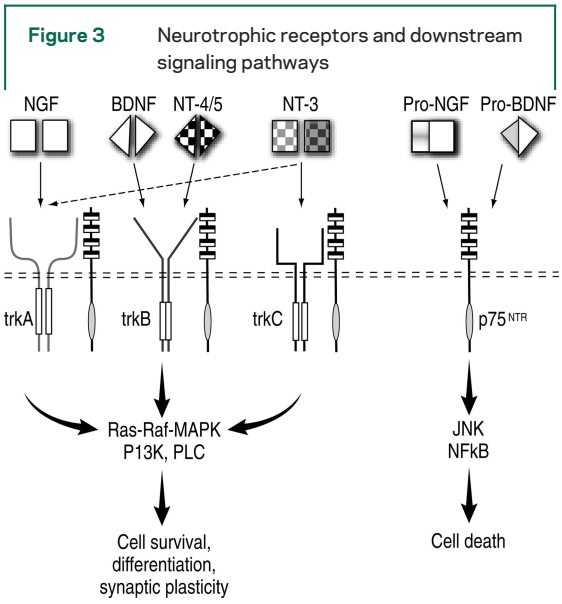


Figure 3 Neurotrophic receptors and downstream signaling pathways

Mature forms of neurotrophins bind to cognate Trk receptors and $p75^{NTR}$, promoting cell survival, differentiation, and synaptic plasticity (left). Proneurotrophin forms of NGF and BDNF bind to $p75^{NTR}$, promoting cell death (right). BDNF, brain-derived neurotrophic factor; JNK, Jun N-terminal kinase; MAPK, mitogen-activated protein kinase; NFkB, nuclear factor kappa B; NGF, nerve growth factor; NT, neurotrophin; $p75^{NTR}$, p75 neurotrophin receptor; trk, receptor tyrosine kinase. Adapted from Pezet and McMahon,[24] with permission.

phin (proneurotrophin or mature neurotrophin) and the class of targeted receptor (Trk or p75). At present, it is still unclear whether the survival actions or apoptotic actions of neurotrophins predominate and under which physiologic conditions either response is favored.

GDNF. Ligands of the GDNF family (GFL)—GDNF, neurturin, artemin, and persephin—promote central and peripheral neuron growth and differentiation. GDNF protects dopaminergic neurons in animal models of Parkinson's disease and promotes motor neuron survival in vivo. This factor also has a number of nonneural functions, which range from regulating kidney development to mediating spermatogonial differentiation.[22] Persephin is neuroprotective in ischemia in animal models.[29]

GFLs signal through the RET ("rearranged during transfection" proto-oncogene) receptor tyrosine kinase. To activate this pathway, GFLs must first link with a second protein class, the GDNF family receptor-α (GFRα) receptors, which in turn bind to the RET plasma membrane. Four such GFRα receptors have been characterized, and these determine the ligand specificity: GDNF binds to GFRα1, neurturin to GFRα2, artemin to GFRα3, and persephin to GFRα4. In addition to these high-affinity interactions, more promiscuous bindings between GFLs and GFRαs have been observed.[22]

Like the NGF family ligands, GFLs also function in the immune system and are expressed by immune cells.[7] Vargas-Leal et al. reported that human $CD4^+$ and $CD8^+$ T cells, B cells, and monocytes express neurturin transcript and protein. These immune cells also express RET and of the GFRαs, mainly GFRα2, allowing formation of the GFRα2–RET complex. The addition of GDNF or neurturin to activated peripheral blood mononuclear cells reduced the amount of detectable TNF protein without altering its transcription.[7] These findings suggest that intercellular communication among immune cell populations may be mediated by neurturin. The import of various neurotrophic and neuroprotective factors by infiltrating immune cells may thus provide a molecular explanation for the dual role of inflammation in CNS diseases.

FUNCTIONAL NEUROPROTECTIVE EFFECTS OF AUTOANTIGEN-SPECIFIC T CELLS "Protective immunity" is a term first used by Schwartz et al. to explain how T cells specific to a CNS self-antigen, such as myelin basic protein (MBP), may protect damaged neurons from secondary degeneration.[3] Although anti-MBP T cells are potentially encephalitogenic, these cells are also found in the immune systems of healthy subjects.[30,31] To determine whether accumulating T cells exert a beneficial or deleterious effect after axon injury, Moalem et al.[3] injected anti-MBP T cells into rats that experienced injury to the optic nerve. Compared with control rats, anti-MBP-injected rats maintained about 250% more retinal ganglion cells with functional axons. Electrophysiologic analysis suggested that the neuroprotective effect of the anti-MBP cell clones was due to a transient reduction in energy requirements, which caused a temporary state of inactivity in the damaged nerve. However, the investigators also considered other explanations, such as the expression of growth factors by anti-MBP cells.

As noted previously, studies with human immune cells demonstrated that CNS-specific T cells secrete neurotrophin family members such as BDNF,[6,12,27] as well as the GFL neurturin.[7] The expression of neurotrophic factors by immune cells may thus play an important role in mediating neuroprotective immunity in CNS diseases such as MS. Furthermore, the "neurotrophic cross-talk" between the immune and nervous systems might also contribute to the therapeutic effects of certain immunomodulatory therapies (see below).

Subsequent studies, mainly in Lewis rats with spinal cord injury (SCI), provided further support for the neuroprotective role of CNS autoreactive T lymphocytes.[32,33] In addition, Hammarberg et al.[34] reported that T and natural killer (NK) cells in the spinal cord of rats with EAE produced BDNF, NT-3, and GDNF, and can reduce the extent of neuron injury after ventral root avulsion. These authors also found that bystander-recruited NK and T cells displayed similar or increased neurotrophic factor levels compared with the anti-MBP T-cell populations. Recently, Ziv et al.[35] showed that hippocam-

pal neurogenesis could be restored in mice with SCI by the transfer of CNS-reactive T cells. These T-regulatory lymphocytes were also necessary for the completion of spatial learning and memory tasks and, notably, for BDNF expression in the dentate gyrus.

In contrast, a series of studies by Jones et al.[36,37] challenged the notion that autoreactive T lymphocytes minimize neuronal and glial cell death after CNS injury. These authors reported that transgenic mice (>95% $CD4^+$ MBP-specific T cells) with SCI experienced impaired recovery of locomotor and reflex function, compared with nontransgenic mice. This impairment correlated with aggravated demyelination and axon loss, along with increased expression of proinflammatory cytokines.[36] MBP-immunized rats with SCI also showed functional disability, aggravated lesion injury, increased rubrospinal neuron loss and intraspinal T-cell accumulation, and greater release of macrophages versus controls.[37] The investigators were unable to observe neuroprotection or functional improvement in MBP-immunized rats,[37] and therefore concluded that myelin-reactive T cells are pathologic effector cells that impair recovery and exacerbate tissue injury at and beyond trauma sites.

These discrepancies illustrate an important point: The net effect of inflammation depends crucially on the experimental setting. Immunostimulation in one setting may lead to net neuroprotection, whereas immunostimulation in a slightly different setting (or on a different genetic background), which favors an encephalitogenic immune response, may lead to net neurodestruction.

NEUROPROTECTIVE POTENTIAL OF IMMUNOMODULATORY THERAPIES There is increasing evidence that MS has a distinct neurodegenerative component even early in the disease course. An extreme view even holds that MS is primarily a degenerative rather than an inflammatory disease. It is more likely, however, that degeneration is secondary to inflammatory injury. In any event, neuroprotection is increasingly appreciated as a valid therapeutic goal. It is reasonable to assume that all of the currently used immunomodulatory and immunosuppressive therapies, including interferon (IFN)-β, glatiramer acetate (GA), natalizumab, and mitoxantrone, have some indirect neuroprotective effect by reducing the extent of immune-mediated injury to myelin, which in turn protects axons and neurons.

Primary neuroprotective therapies are increasingly being studied in animal models of MS, but these therapies are still in their infancy with respect to human MS.[38] In addition, some of the currently used immunomodulatory agents may have a neuroprotective component, e.g., by enhancing the expression of neurotrophic factors in the CNS. Such a mechanism was first suggested for GA, which shifts the cytokine profile toward an anti-inflammatory Th2 type[39,40] and reduces the activation threshold of monocytes.[41] In addition, GA enhances the production of neurotrophic factors. Drug-specific T-cell lines, which represented the major Th cell phenotypes, produce BDNF in addition to Th1- or Th2-related cytokines.[6,42] Recognition of crossreactive antigens at the plaque site may be required to reactivate T cells, which then release neurotrophic factors.[41] Indeed, the immunomodulator GA augments the expression of neurotrophic factors in brains of experimental autoimmune encephalomyelitis (EAE) mice[43] and *N*-methyl-phenyl-tetrahydropyridine (MPTP) rats.[44]

CONCLUSION During the past decade, a burgeoning body of evidence has demonstrated that inflammatory reactions in the CNS have a dual nature: they may be neuroprotective as well as neurotoxic. These studies illustrate that the nervous and immune systems have overlapping rules of organization and intercellular communication. As a result, both systems express a host of common cytokines and neurotrophic factors that regulate cell survival and function. These shared mediators enable the two systems to engage in cross-talk and may provide a molecular explanation for neuroprotective effects of inflammation, which have been observed in animal models of CNS inflammation and trauma.

This dual role of inflammation also impacts our view of the pathogenesis and treatment of MS. The evidence suggests that both the harmful and the beneficial components of CNS inflammatory processes contribute to lesion development. It is the cumulative effects of neurotoxic and neuroprotective mediation that determine which way the scales swing in any given pathologic situation.

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