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Guest Editorial

Neural immunity: Friend or foe?

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The articles compiled in this special edition of *Journal of NeuroVirology* target a developing field of investigation seeking to uncover how the immune system affects both the pathogenic process and protection against the ravages of neurodegenerative processes. Whether caused by a microbe, trauma, toxic metabolite, autoimmunity, or part of a wide degenerative process, immune dysfunction commonly affects central nervous system (CNS) disease. All together, the work presented here proved to be a unique undertaking with contributing scientists outside the field of neurovirology. Indeed, multiple disciplines including molecular neuroscience, neuroimmunology, virology, cellular immunology, receptor pharmacology, neuronal electrophysiology, neurochemistry, clinical neurology, and development neurobiology were joined.

The basis of this work rests with the hypothesis that brain mononuclear phagocytes (MP; perivascular and brain macrophages and microglia) act as inducers of disease by engaging the immune system to protect, defend, or induce neural injury. Indeed, it is the brain MP that act as scavengers killing microblial pathogens, regulate immune responses through antigen presentation and mobilization of adaptive immune activities, and affect the production of neurotrophic or toxic secretory factors that incite disease processes. For many years, these responses were thought to be reactive to ongoing disease mechanisms with little effects on disease itself, let alone repair. The works compiled in this issue demonstrate quite clearly this is no longer true. Immune responses cannot be directed only against a microbe but also against self-antigens that are expressed in damaged CNS, leading to innate neurotoxic or adaptive anti-self immunity that commonly follow viral infections. Importantly, therapeutic modalities may take advantage of CNS immune responses through vaccination generating neuroprotection. Together, these articles serve to bring together common neuroimmune links between highly divergent diseases (for example, Parkinson's and Alzheimer's disease and human immunodeficiency virus type-one dementia). In the end, I hope this work will serve as discussion points for future collaborations and began to break down the barriers of disease, enabling targeted research activities toward what we have in common. *Journal of NeuroVirology* (2002) **8,** 474–479.

Introduction

Classically, neural inflammation has been thought to be a consequence of infectious agents that have invaded the central nervous system (CNS) (reviewed in Gendelman and Folks, 1999). Indeed, acute immune responses are elicited following direct attack on the brain by virus and other microbes that commonly include measles, herpes, tuberculosis, polio, and the human immunodeficiency virus (HIV). Each elicit debilitating neurological disease. Interestingly, despite the exceedingly complex biological and structural make up of the CNS, it has

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a limited repertoire for its own protection and response to disease-causing injuries. Even so, it has the capacity to engage the peripheral immune system to eliminate infection and toxic/metabolic processes. The brain has several protective mechanisms. First, its own protective shield, the blood-brain barrier (BBB), and second its lack of a conventional lymphatic drainage system. Both serve to prevent or restrict movement of cell and macromolecules inside the CNS. Third, it has its own immunoregulatory cells that include endothelial cells, microglia, astrocytes, and oligodendrocytes. These cells serve to protect and nourish the brain and to maintain its homeostasis. Pivotal to these functions are the glia (notably, microglia and astroglia). Both serve to protect the brain from damaging inflammatory responses. Glial cells, under steady-state conditions, present antigen, express major histocompatibility complex (MHC) class I and II, regulate production and uptake of excitotoxins (for example, glutamate), and secrete trophic factors that nurture nervous system cells and protect their critical functions (reviewed in Gendelman *et al*, 1999).

During disease, the nurturing response of glia turns deadly and the cells evolve into a principal foe of the CNS. Functional changes that occur in glia include MHC class II induction. This follows a broad range of insults to the CNS as trauma, ischemia, infection, inflammation, and neurodegeneration. Moreover, glial cells and principally microglia secrete toxic factors and include pro-inflammatory cytokines (for example, tumor necrosis factor alpha [TNF-γ] and interleukin beta [IL-1γ]), quinolinic acid, arachidonic acid and its metabolites, nitric oxide [NO], platelet activating factor [PAF], γ and γ chemokines excitatory amino acids, and free radicals. This occurs as a reaction to the disease process and participates in cell damage by direct microbial infection, inappropriate cell signaling, receptor ligand interactions, or initiating an adaptive peripheral immune response. The process can be accelerated, as the same events that affect neuroimmune activation can also influence leukocyte migration into and through the brain. Overall, whether or not the immune responses perpetuate or attenuate disease depends on the intracellular signaling pathways elicited; the balance between trophic and toxic factors, Th1 and Th2 lymphocyte responses, the immunogen, the ongoing degenerative processes, the brain region, and its susceptibility to the noxious insult.

We have learned how immune reactions occur in the CNS through studies of viral infection and/or brain autoimmunity. This, in many ways, has laid the groundwork for what is described in this issue. Briefly, activated T cells penetrate the BBB after insult to the CNS and can initiate both protective and toxic inflammatory responses. Protective responses are elicited through elimination of the ongoing infectious agent by innate, humoral, and cytotoxic immune activities. Nonetheless, wide-spread inflammation often leads to damage to the BBB and the further transendothelial migration of leukocytes entering the nervous system. Such cells can easily encounter and engage perivascular macrophages through direct cell-to-cell contact (mediated through CD40) or through soluble factors released (for example, interferon gamma, [IFN-γ]). This leads to activation of brain mononuclear phagocytes (MP; perivascular and brain macrophages and microglia) and an amplification (by paracrine and autocrine mechanisms) of inflammatory cell responses throughout the CNS region involved. Activated microglial and/or astroglial reactions ensue, which can affect neurodegenerative processes or enhance other MP functions such as phagocytosis, intracellular killing, antigen presentation, and secretory neurotoxic activities. Most importantly, regardless of the insult, such mechanisms are operative in a wide variety of diseases. In closing this introduction, one freely admits that the pathogenesis of the diseases discussed cannot solely be explained by alterations in immune function. However, it is the balance between the degenerative process and the reactions developed against it that serves to explain the pathological outcomes and will likely lead to therapeutic measures where few are now available.

The immune system in brain homeostasis, response to injury, and tissue repair

This first section of the special issue addresses the role of neural immunity in tissue homeostatis, in affecting cellular immune responses, and, most importantly, in directing repair toward a wide range of neurodegenerative and autoimmune disorders. Clearly, during steady-state, the brain's innate immune system and those circulating leukocytes that reach it are designed to maintain the structural and functional integrity of the nervous system. It is also widely agreed that such functional breakdown during disease leads to neurotoxic activities. These have a profound influence on the pathogenic processes of many neurodegenerative disorders, including autoimmune diseases.

Studies by Michal Schwartz and colleagues are reviewed in this issue (Schwartz, 2002) and provide a unique insight into the role that immune cells play in protecting injured nervous-system tissue. This may occur through limiting the effects of normally "destructive" innate immune factors (including pro-inflammatory cytokines, chemokines, free radicals, quinolinic acid, arachidonic acid and its metabolites, and excitatory amino acids, among others) or by bringing into or inducing protective or nurturing products to the area of tissue damage. In this scenario, the immune response is directed against dominant self-antigens residing in damaged tissue where adaptive anti-self immune responses support the protective activity of local resident cells by bringing regulatory factors that modulate harmful innate immune

function (neurotoxic activities). It is thought that, since the specificity of this autoimmune response depends more on where the lesion occurs than the type of insult, the response could be strongly affected by therapeutic vaccination. The most provocative aspect of this theory is the idea that protective autoimmunity would occur irrespective of the primary etiology of the neurodegenerative process and would thus be broadly applicable for CNS disease. Indeed, the end result is that immunity directed to nervous system degenerative disorders could be harnessed to ameliorate disease by vaccine strategies. However, this is not the only functional tie between the immune and CNS systems.

In the second article, by Havilioglu *et al* (2002), a number of neuronal guidance cues found in the CNS have been recognized, which include the family of secreted proteins that affect biological processes parallel to the named chemokines. These are Slit proteins, which can guide the movement of at least two populations of migrating neurons, those from the anterior subventricular zone to the olfactory bulb and those moving from the striatal primordium to the neocortex. Slit proteins have clear functional similarities among chemokines; thus, they provide critical linkages between the immune system and neuronal function (Havilioglu *et al*, 2002). The Slit protein, a chemorepellent, affects both axon and neuronal migration and suggests that conserved guidance mechanisms exist for neurons and leukocytes. Functional interactions between Slit and chemokines require roundabout receptor (Robo) for Slit and the seven transmembrane receptors coupled to G proteins or G protein-coupled receptors (GPCRs) for the chemokines. Havilioglu and colleagues propose that, because Slit is not unique among the neuronal guidance cues, other similar molecules may play a role in modulating the migration of leukocytes. The finding of Slit inhibition signaling through chemokine receptors, including CCR5 and CXCR4, suggests a possible application of Slit in the treatment of HIV-1 infection. This would occur by modulating viral proteins mediating neuronal destruction through chemokine receptors expressed on neural cells. Studies of the crosstalk of signaling pathways between Robo and GPCR in affecting neural function are underway and may provide unique insights into the common mechanisms of cell function between leukocytes and neurons.

Continuing on this theme of common protective or degenerative links between the immune and CNS tissues is the work of O'Keefe and Benveniste (2002). These investigators review the importance of MHC II in brain homeostasis and disease. Clearly, class II MHC genes, which encode heterodimeric cell surface glycoproteins, present fragments of processed foreign antigen to lymphocytes and play a central role in the initiation of T cell-mediated immune responses. A wide variety of cell types can present antigen. Aberrant expression of class II MHC can have untoward consequences on the host, leading to the development of autoimmunity and affecting neurodegenerative processes. IFN-γ-activated microglia and brain macrophages express class II MHC, the costimulatory molecules B7 and CD40, and serve as the major antigen presenting cells in the CNS. In CNS diseases such as Multiple Sclerosis (MS), Parkinson's and Alzheimer's disease (PD and AD), and HIV-1-associated dementia (HAD), prominent expression of class II MHC molecules has been detected on microglia and macrophages. The expression of class II MHC and other costimulatory molecules by brain MP allows them to activate naïve, autoreactive $CD4^+$ T cells and to restimulate memory cells, leading to inflammation and demyelination. MP are clearly implicated in both the initiation and perpetuation of inflammation in the CNS, as well as the possible neuroprotective and/or regenerative responses developed previously by Schwartz (2002).

The concluding article of this section supports this theme and deals with what happens when a pivotal regulatory molecule for tissue homeostasis turns foul. A case in point is glucocorticoids (GCs), a major defense-to-stress pathway for tissue homeostasis and in disease (reviewed by Dinkel *et al*, 2002). Under steady-state conditions, GCs promote homeostasis and are essential for host survival. On balance, it has been found that, when exposure to GCs occurs in excess and for prolonged time periods, they can induce serious negative effects on target tissues. This occurs in a manner distinct from their metabolic side effects. For example, sustained exposure to GCs can lead to impairment of cognitive function and promote brain atrophy. This, importantly, includes dendrites of pyramidal neurons in the CA3 region of the hippocampus, a cognitive functional brain region. Magnetic resonance imaging studies in humans support this contention and show that GC-related conditions (for example, Cushing's disease and post-traumatic stress) are associated with hippocampal atrophy. GCs can also impair neuronal survival during diverse CNS insults including ischemia, trauma, seizure, HIV-1 infection, and beta-amyloid (Aγ), among others. Moreover, although GCs have been used effectively as therapies for edema from brain tumors, viral encephalitis, bacterial meningitis, and acute exacerbation of MS, it can affect immune function. One of the key focal points of the Dinkel review (2002) is that GCs are not always anti-inflammatory but can be pro-inflammatory and in this way affect neural function and CNS homeostatic responses.

All together these articles strongly support the concept that peripheral and CNS immune regulatory responses can, in various situations, perform both ameliorative and toxic roles for disease. Underlying all of this is the challenge for future investigations—to determine how to harness neural immunity to retard or perhaps abrogate disease by focusing immune responses toward the amelioration of disease and its devastation, regardless of cause.

Immunology of neurodegenerative disorders

The second component of our special issue deals with the immunology of neurodegeneration. The focus is on two of the most common and debilitating disorders of the CNS, namely AD and PD. McGeer and McGeer (2002) show strong evidence for the association between a state of chronic CNS inflammation and AD pathogenesis. The key actor in the process is, once again, the activated resident-brain MP. The function of these cells in neural immunity and CNS health and disease cannot be over stated. Indeed, MP products including cytokines, chemokines, and excitotoxins, together with proteins of the classical complement cascade and pentraxins, play a critical if not central role in the pathogenesis of AD. Innate microglial neurotoxic responses affect neurons significantly as a result of the vulnerability of these postmitotic cells. In further support of this idea is the epidemiological evidence demonstrating a role of nonsteroidal, anti-inflammatory drugs for impeding the onset and progression of AD. This epidemiological data provides a link that chronic inflammation is important in AD pathogenesis. Since non-steroids strike at the periphery, the authors suggest that better clinical results may be found if new therapies that inhibit microglia activation or the complement system *per se* in the CNS are discovered.

In the article by Mattson (2002), the importance of CNS inflammation in AD pathogenesis is extended in several ways. First, parallels are drawn between AD and known infectious diseases of the nervous system that produce neurodegeneration. For all diseases described, alterations in peripheral immune function are found. The potential of boosting immune responses to augment disease progression remains a viable treatment or preventive option for AD, HIV encephalitis (HIVE), and perhaps for prion disease as well. The linkage among these seemingly divergent disorders of the brain is in neuronal damage and the role of toxic proteins; Aγ in AD, HIV-1 gp120, nef and tat in HIVE, and prion protein in Creutzfeld-Jacob disease. In addition, common downstream mechanisms for neurotoxicity involve glial innate immunity including oxidative stress and disruption of calcium homeostasis. Ultimately, these processes lead to neuronal excitotoxicity, apoptosis, and/or necrosis. Peripheral immune dysfunction also occurs in these diseases. Specifically, persenilin and the amyloid precursor protein (APP) mutations in AD affect oxidative stress and lymphocyte calcium signaling, leading to changes in pro-inflammatory cytokine production and, to varying degrees, the regulation of adaptive immune responses. Similar findings in regards to glial innate immunity have been shown in mouse models of AD. The most recent and exciting work in how immune responses can affect disease pathogenesis is found following Aγ-peptide immunization in AD mice. Such an immunization strategy amyloid from the brain and ameliorate of memory deficits. All together, Mattson (2002) provides a very strong argument that neural immunity can have both a positive and negative effect on disease progression for AD.

Such a concept also underlies the pathogenesis of PD (Wu *et al*, 2002). PD, distinct from AD in many ways, is nonetheless a quite-common neurodegenerative disorder associated pathologically with progressive loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc). Interestingly, this neuronal loss occurs concomitantly with a glial innate immune response. Like in AD, brain MP and specifically microglia appear to be the major players in disease, but astrocytes may also be involved. Indeed, the loss of dopaminergic neurons in postmortem PD brains is associated with microglial activation. This response is more significant in the SNpc than in the striatum, where neuronal cell bodies are lost. Activation of microglial cells also plays in the pathogenesis of animal models of PD. In the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) toxin-treated animals, microglial activation is prominent and occurs reaching maximal levels before dopaminergic neurons are lost and before astroglial responses are seen. Such glial responses in PD may attenuate the neurodegenerative process. For example, glial-derived neurotrophic factor (GDNF) supports SNpc dopaminergic neuronal survival in MPTP intoxicated animals. In addition, astrocytes may avidly take up extracellular glutamate and mitigate the harmful effects of subthalamic excitoxic input to the SN. This, combined with the susceptibility of SN neurons to microglial toxins, support, the notion that changes in secretory profiles of glia may play an important role in the pathogenesis of PD. Once again, it is the balance between a glial neurotoxic and trophic response in PD that results in induction or protection against disease, mediated principally by oxygen free radicals, pro-inflammatory cytokines, arachidonic acid and its metabolites, and, among others, the cast of immune characters that underlie the disease process in most neurodegenerative disorders.

Chemokines and their receptors in CNS protection and disease

The survival of the organism requires response to injury or infection and, in vertebrates, is carried out by the immune system, necessitating immune cell trafficking to areas of tissue damage. A critical process regulating such events is chemokines or chemotactic cytokines. Indeed, chemokines and their receptors have been shown to play a critical role in the inflammation underlying natural immunity against microbial pathogens, as well as those following trauma and toxic/metabolic disease processes. These same proteins and their receptors are also widely expressed in the nervous system by neuronal and glial cells,

among others. Although the precise function of these factors have not yet been realized, they appear to be critical for the development of the nervous system for the regulation of neuronal function (excitability and synaptic transmission) and in the pathogenesis of neurodegenerative, autoimmune, and infection brain disorders (Cho and Miller, 2002). The discovery that chemokines and their receptors are involved in the pathogenesis of a variety of CNS pathologies has defined their role in disease and neuroinflammatory responses (Ragozzino, 2002). Indeed, numerous reports have shown that both glia and neurons are capable of expressing both chemokines and their receptors, especially after inflammatory stimuli (reviewed in Ragozzino, 2002). In the reports by Cho and Miller, 2002, and Ragozzino, 2002 the effects of CXC chemokines receptor stimulation on the CNS and regional brain demonstrates their functional role in developmental neurobiology, in homeostasis and for disease. Indeed, expression of most or all of the γ and γ chemokine receptors by neurons and glia has been reported along with laboratory, animal model, and clinical reports of their importance in diseases of the CNS. Cotter and colleagues (Cotter *et al*, 2002) explore one chemokine in quite strong association with neurons. Fractalkine (FKN; present in membrane-anchored and soluble isoforms) participates in the generation and progression of inflammatory processes of the nervous system. Upon binding to its receptor (CX3C), FKN induces adhesion, chemo attraction, and activation of leukocytes and demonstrates the fact that neurons, along with glia, participate in neuroinflammatory responses, a concept not well accepted until very recently.

Innate and adaptive immunity in viral neuropathogenesis and disease protection

During ongoing viral infection of the CNS, a number of innate and acquired immune factors contribute, in a significant manner, to neural cell damage. Viral and/or cellular proteins can damage brain cells by both direct and indirect mechanisms. In contrast, viruses (for example, rabies and herpes simplex virus type one) can directly destroy neurons and/or glia, leading to cell death by cytolytic infection. More commonly, (for example, cytomegalovirus, Borna, and HIV) infection of the brain involves activation of innate immune responses resulting in subacute and chronic disease mediated by the same glial factors, including pro-inflammatory cytokines, free radicals, excitotoxins, and arachidonic acid and its metabolites, among others operative in most neurodegenerative disorders (see above). Typically, MP is the primary effector of these immune neurotoxic responses. Indeed, for HIV-1, the major reservoir for productive viral replication in the CNS is the MP. These same cells are the source of cell products that affect or retard the neuropathogenic process that follows viral infection in its human host. How viral replication is regulated by MP, how it induces neurotoxic activities, and how ultimately it may also affect the regulation of trophins are the key focal points of this section on neurovirology and neuroimmunity.

The work by Iqbal Chowdhury and colleagues (Chowdhury *et al*, 2002) seeks to define cellular-based antiviral immunity regulated by MP. Here, the site of restriction in lymphotropic (X4) HIV-1 infection of MP is prior to expression of mature capsid antigen p24 and production of cell-free infected viral particles. Restriction of macrophage tropic viruses for infection of macrophages can also occur, but in a very distinct manner. Here chemokines and cytokines are synthesized and released after HIV-1 R5 infection. This occurs through the rapid secretion of TNF-γ macrophage inflammatory protein 1γ (MIP-1γ) and Regulated upon Activation Normal T-cell Expressed and Secreted (RANTES). Each of these cytokines and/or chemokines has been shown both to be up-regulated in the brain tissue of infected people and to control virus infection in laboratory studies of virus-cell interactions. The Chowdhury (2002) studies elegantly serve to demonstrate how host MP immunity can affect ongoing viral infection by both classes of viral strains and by different mechanisms in the same cell within its host.

One of the pivotal cytokines discussed by Chowdhury (2002) and induced by HIV-1 infection of brain MP is TNF-γ. This is developed in some detail by Perry *et al* (2002) in an article focused on how one cytokine could produce very different effects dependent on where, how, and when it is released in the human host. Indeed, in recent years, TNF-γ has been shown to have a significant role in neural function. Under steady-state conditions, TNF-γ is an important modifier of thermoregulation and the hypothalamic–pituitary–adrenal (HPA) axis. TNF-γ also has neuromodulatory and neuroprotective effects under distinct sets of conditions. In contrast, in diseased and inflammatory brain tissue, TNF-γ, when produced in abundance, has toxic affects on neurons. The authors explain that TNF-γ exerts such effects by interfering or potentiating signaling of growth factors (dependent on concentration and region) or by affecting the regulation of other cytokines either at the receptor levels, at downstream signaling pathways, or by intraneuronal receptor crosstalk. At the receptor level, either through receptor location or density, or activation of rote, predetermined sets of cellular signaling cascades. This occurs either in paracrine fashion, between receptors on interacting cells, or in an autocrine fashion between receptors on the same cells.

In the concluding article, Langford and Masliah (2002) explore how the host, in response to cellular damage, can produce trophic factors that serve to

protect neural cell populations. This details how the innate immune response by glia may not always be harmful, exploring how both neurotrophic and angiotrophic factors can modulate neuroimmune activities and affect the pathogenesis of neurodegenerative disorders. Cytokines and chemokines produced by virally infected cells are amplified by autocrine and paracrine cellular responses and can affect neural function at areas far removed from where infected cells are found, in the case of viral infections of the CNS. Viruses can exploit the host's immune system through molecular mimicry in which virus borrows host proteins and inhibits host factors, allowing viral evasion of immune defense. It is thought that crosstalk signaling among host cells and the immune system may influence cell fate by producing trophic factors that protect neurons against virus-mediated damage. Thus, taken together, trophic factors may be produced by viral-infected cells or by inhibiting or promoting viral replication. They may affect the tempo of disease by antagonizing excitatory amino acid activity, regulating glutamate receptors, or by maintaining blood-brain barrier integrity.

Conclusions

The immune system is a simply incredible defense machine, providing a developed organism the means to make specific, rapid, and protective responses against pathogenic microorganisms. In CNS diseases, there is ample evidence that such a protective immune response can turn against the host, leading to significant morbidity and mortality from a range of insults. This fact has been demonstrated in a number of immunopathologic and degenerative disease conditions. Clearly, neurodegenerative and neuroviological disorders show deficits in innate immune responses and often give rise to neural cell destruction with accompanying cognitive, motor, and/or behavioral deficits in affected humans. The involvement of the microglial cell is clearly mediated through the production of oxygen-free radicals, pro-inflammatory cytokines, and chemokines; NO; arachidonic acid and its metabolites; quinolinic acid; and excitotoxins. Such deficits in innate immunity shown in a variety of CNS diseases with varied pathogenic mechanisms and etiologies. However, just as effective immunity could be martialled by vaccination serving to protect against microbial pathogens, vaccination against self-antigens may also reverse a harmful process into a protective one for CNS disease. The key to understanding and, ultimately, in providing realistic long-term solutions to a number of microbial and non-microbial diseases of the CNS is how to best focus the immune response; inevitably, how to turn a foe into a friend. Clearly, neural immunity may provide the key to the development of effective means to treat the untreatable and perhaps to prevent a broad range of diseases. This exciting and developing area of research is, at the end of the day, what lies before those who pursue this area of research.

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