Immune mechanisms in neurological disorders: protective or destructive?

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The VIth Congress of the International Society of Neuroimmunology was held in Edinburgh, Scotland from 3–7 September 2001.

Applying immunological methodology to neurological science has highlighted interesting interactions between immune and nervous systems, and shown that immune mechanisms are important in a wide range of neurological disorders and their treatments. Many disorders of the peripheral and central nervous systems (i.e. neurodegenerative brain diseases, trauma to the brain and spinal cord, and neurological tumors) involve activation of the immune system. The meeting covered the variety of immune mechanisms involved and the potential targets for immunotherapy of a diversity of disorders, including multiple sclerosis (MS) – the most well-characterized of the neurological diseases – and its animal model [experimental allergic encephalomyelitis (EAE)], myasthenia gravis (MG) and Guillain Barré syndrome, HIV and AIDS dementia, and Alzheimer's and prion diseases.

Infection

What is the role of infection in neurological disease? D. Griffin (Baltimore, MD, USA) noted that neurons, microglia, astrocytes and oligodendrocytes are all potential viral hosts in the central nervous system (CNS). Many types of virus induce cell death and the immune response must maintain a careful balance between preventing apoptosis (particularly important for neurons) while controlling viral persistence. In some cases, the association between infection and disease is simple; for example, latent infection of human ganglia neurons with varicella zoster virus can result in various neurological disorders, as well as the more-common peripheral manifestation of shingles (D. Gilden, La Jolla, CA, USA). For other cases, the etiology is less clear. S.D. Miller (Chicago, IL, USA) discussed how epitope spreading and molecular mimicry might trigger autoimmunity. This theory was supported by evidence from J. Griffin (Baltimore,

MA, USA) that in Guillain Barré syndrome, anti-ganglioside antibodies (Abs) probably arise secondary to *Campylobacter* infection.

Effector molecules

Antibodies

In the opening lecture of the congress, J. Newsom Davis (Oxford, UK) highlighted the pathogenic role of anti-acetylcholine receptor (AChR) Abs in myasthenia gravis (MG). Passive transfer of Abs can transfer disease, and if maternal Abs are directed against the fetal AChR γ-subunit, the baby can become paralyzed even in the absence of maternal symptoms. Proteins of the presynaptic membrane are targets also for autoAbs in other syndromes (e.g. Lambert–Eaton syndrome). Similarly, M. Levite (Rehovot, Israel) summarized evidence that anti-glutamate receptor (GluR) Abs are associated with epilepsy in Rasmussen's encephalitis. Many other autoAbs have been associated with neurological disease, including anti-dsDNA and anti-cardiolipin Abs, although the pathogenicity of these Abs is less clear. Abs to some intracellular CNS targets are markers for CNS disease, particularly, when associated with certain cancers that express the neuronal target, but are not themselves pathogenic (R. Darnell, New York, NY, USA). These data raise several important issues for disorders of the CNS: does autoimmunity or CNS disease come first; and does autoimmunity inevitably cause disease or are other factors involved?

Matrix metalloproteinases

Matrix metalloproteinases (MMPs) can mediate neuroinflammatory disease through damage to the blood–brain barrier (BBB), breakdown of myelin, processing of cytokines and tissue remodeling (B. Kiesier, Graz, Austria). For example, gelatinase B (MMP9) is a marker of neuroinflammation and it can cleave myelin basic protein (MBP) to an immunodominant epitope, possibly, resulting in an autoimmune reaction (G. Opdenakker, Leuven, Belgium)[1]. However, MMPs are also important

during remyelination and/or regeneration. MMP9 is required for process outgrowth by oligodendrocytes and MMPs might terminate inflammation (B. Kiesier). N. Woodroofe (Sheffield, UK) discussed the contradictory roles of ADAM17 in MS. Is the release of membrane-bound tumor necrosis factor (TNF), by ADAM17-mediated cleavage, detrimental (recruitment of immune cells and oligodendrocyte toxicity) or beneficial (protective against demyelination)? Tissue plasminogen activator can also mediate both axonal protection – by removal of fibrin deposits – and cell death (D. Gveric, London, UK). The beneficial aspects of MMPs in CNS repair and regeneration were highlighted by V. Wee Yong (Calgary, Canada). Extensive tissue remodeling is required for oligodendrocyte-mediated myelination, suggesting the involvement of proteinases. MMPs might be involved also in axonal elongation and guidance, through the release of matrix-bound growth factors, remodeling of physical matrix barriers and interactions with ephrin.

Complement

Two major effector events of the complement cascade are the opsonization of foreign particles and the lysis of cells by the membrane attack complex (MAC). It has long been known that in scrapie-infected sheep, there is an accumulation of infectivity in the spleen before the CNS. Prion protein accumulates in follicular dendritic cells following opsonization by complement (N. Mabbott, Edinburgh, UK). The MAC might be responsible for demyelination and axonal damage in MS and EAE. C6-deficient rats do not suffer demyelination following administration of an anti-MBP Ab (R. Mead, Cardiff, UK). Myelin-induced EAE in C5-deficient mice comprised focal, noninfiltrative lesions, with less demyelination than controls (S. Weerth, Baltimore, MD, USA). *In vitro*, neurons are very susceptible to complement because they express low levels of complement regulators. Modulating their level of expression might be a potential therapeutic strategy;

Key outcomes of the meeting (protective and destructive aspects of immunity in the CNS)

- The full range of immune mediators can be involved in neurological disease – in both protective and destructive roles.
- Epidemiological and experimental evidence suggests an infectious etiology for some forms of neurodegeneration.
- Abs directed against brain targets can cause autoimmune damage, but therapeutic Abs might be used to generate tolerance to autoAgs or inhibit neurodegeneration due to extracellular plaques.
- MMPs play a role in both destruction and regeneration.
- Complement can cause damage in the CNS by opsonization and MAC-mediated lysis.
- Inflammatory cytokines are not necessarily harmful. In some cases, an inflammatory response might be beneficial.
- Phagocytic cells in the CNS (macrophages and microglia) can be neurotrophic or neurotoxic, depending on the environment.
- Both CD4^{+} and CD8^{+} T cells are recruited to the inflamed brain by chemokine gradients. Their relative importance and effects depend on local conditions.

transfection of IMR32 cells to express decay accelerating factor conferred protection from complement activation and lysis (J. van Beek, Cardiff, UK).

Cytokines

The level and type of cytokines produced during brain pathology must have a significant impact on neuronal disease. Research in this area has focused on the pro- and anti-inflammatory actions of cytokines. Pro-inflammatory cytokines have been considered traditionally to be harmful. For example, TNF-α contributes to the breakdown of the BBB in EAE and has direct cytotoxic effects on oligodendrocytes (G. Scott, Philadelphia, PA, USA); interferon γ (IFN-γ) is involved in corona-virus-induced demyelination in mice (S. Perlman, Quebec, Canada); and interleukin-12 (IL-12) accelerates EAE by promoting the induction of T helper 1 (Th1) cells responsible for autoimmune disease (L. Adorini, Milan, Italy). However, an inflammatory response is not always a bad thing. P. Siesjo (Lund, Sweden) discussed the regression of intracerebral tumors mediated by IFN-γ-producing T cells, and T. Seabrook (Boston, MA, USA) presented data showing that the T-cell response to tumors can be enhanced by IFN-γ. Gene therapy to deliver IFN-γ into the CNS has a protective effect for EAE, by increasing T-cell apoptosis through their increased expression of TNFR1 (R. Furlan, Milan, Italy). This challenges the simplistic therapeutic use of anti-inflammatories. Other beneficial effects of cytokines were presented. In cell-transplantation experiments, cells migrate into the white matter tracts in EAE[+], but not naive, rats, in response to a chemotactic gradient of inflammatory cytokines (T. Ben-Hur, Jerusalem, Israel). F. Haour (Paris, France) suggested that the brain IL-1 system (and its effects on the hypothalamic axis) might be defective in autoimmunity, because NZB autoimmune mice have abnormal expression of the IL-1R in the dentate gyrus of the hippocampus. Cytokines might be involved also in the recruitment and differentiation of oligodendrocyte progenitors during remyelination (R. Franklin, Cambridge, UK).

Effector cells

Macrophages and microglia

Macrophages play a crucial role in inflammatory reactions in the periphery, by phagocytosis, antigen (Ag) presentation to T cells and secretion of pro-inflammatory cytokines. To what extent do brain macrophages and microglia mediate similar effects in the CNS? Microglia are activated from their quiescent state in almost all neurological diseases, as a cause or consequence of pathology (H. Perry, Southampton, UK). This has been particularly well studied for HIV-associated dementia (HAD). Mesenchymal monocytic phagocytes are the host cells for HIV in the brain, and their secretion of β-chemokines recruits into the brain and activates additional macrophages. Under steady-state conditions, macrophages are neurotrophic, but during infection with HIV, they become neurotoxic (H. Gendelman, Omaha, NE, USA), giving rise to a positive-feedback loop of inflammation, neuronal loss, and

behavioral and motor abnormalities. HIV-1-infected macrophages are powerful Ag-presenting cells for the generation of anti-viral cytotoxic T lymphocytes (CTLs) but, as H. Gendelman noted, the CTL response might be protective. In HIV-demented individuals, hyperactivated circulating macrophages are recruited to the CNS white matter, where they produce MMP1, which degrades BBB proteins and influences neuronal viability (J. McArthur, Baltimore, MD, USA). There is increasing recognition of the role of neuronal damage in demyelinating lesions, in addition to the large amount of evidence supporting a crucial role for damage to oligodendrocytes (C. Raine, New York, NY, USA). Furthermore, it has been noted that there is a 20% reduction in the number of synapses on motor neurons in MS, which might be caused by microglial separation of pre- and post-synaptic terminals (B. Trapp, Cleveland, OH, USA). However, several researchers have suggested that the close interaction between microglia and neurons, mediated by CD200R–OX2 interactions (J. Sedgwick, Palo Alto, CA, USA), is involved in CNS homeostasis; microglia are activated rapidly by neuronal dysregulation to mount a neurotrophic response (W. Streit, Gainesville, FL, USA). Reactive microgliosis is required for neuron regeneration (W. Streit). Promoting the macrophage response, by manipulating the expression of growth factors, in elderly individuals might promote regeneration of demyelinated areas (R. Franklin).

T cells

The role of T cells in adaptive immunity implies that they will be important for any disease process, by providing help for other cell types, such as Ab-producing B cells, and direct cytotoxicity. The role of CD8^{+} CTLs in neurodegeneration has been given prominence by recent research. H. Neumann (Gottingen, Germany) discussed how activated CTLs are able to cross the BBB and induce apoptosis of neurons through Fas–FasL interactions, and kill astrocytes by the release of cytotoxic granules containing perforin. Although CD4^{+} T cells are involved in organ-specific autoimmunity, most of the cells destroyed in neuropathology do not express MHC class II constitutively. Therefore, CD8^{+} T cells must be involved, as demonstrated by results from the analysis of EAE in CD8-knockout mice

(R. Liblau, Paris, France). Are CD4^{+} or CD8^{+} T cells responsible for the demyelination resulting from corona-virus infection? When CD8^{+} T cells only are present, there is more demyelination but a greater rate of survival (less severe clinical disease), whereas the opposite is true when CD4^{+} T cells only are present (S. Perlman, Iowa City, IA, USA). Yet again, these results emphasize that there is no simple or consistent relationship between a certain response and a beneficial or detrimental outcome. Indeed, G. Plautz (New Haven, CT, USA) demonstrated that CD4^{+} T cells are more efficient than CD8^{+} T cells in the treatment of brain tumors, despite the lack of expression of MHC class II molecules.

T-cell chemokine receptors are involved in the tissue-specific homing of lymphocytes; are there specific brain-homing receptors? T-cell clones from the cerebrospinal fluid (CSF) of MS patients express CC-chemokine receptor 5 (CCR5) and CXC-chemokine receptor 3 (CXCR3) on their surface, and migrate in response to inflammatory protein 10 (IP-10), regulated on activation, normal T-cell expressed and secreted (RANTES) and, possibly, macrophage inflammatory protein 1α (MIP-1α) (M. Marchese, Genoa, Italy). CCR1 and CCR5 might play a role in the recruitment and activation of monocytes in MS lesions (R. Ransohoff, Cleveland, OH, USA)[2]. There is a more pronounced expression of chemokines (e.g. CCL19 and CCL21) and their receptors in the chronically inflamed CNS than in secondary lymphoid organs, which might be responsible for the early recruitment of dendritic cells to the spinal cord observed in murine models of EAE (F. Aloisi and S. Columba-Cabezas, Rome, Italy). C. Brosnan (New York, NY, USA) discussed the function of chemokines expressed by astrocytes at sites of inflammation in regulating the properties of the BBB.

Effective therapy: how long to wait?

Given the complicated genetic and environmental factors associated with the risk of neuroinflammatory disorders, such as MS (G.C. Ebers, Oxford, UK), the prospect of prophylactic therapy for susceptible individuals is a distant dream. Far more realistic is the possibility of therapies aimed to prevent or slow the progress of established disease. Novel techniques for gene-expression profiling, such as fluorescent microarrays, aided by methods of tissue isolation, such as laser-capture microdissection, will identify potential therapeutic targets by comparing expression profiles between diseased and normal tissues (M. Donovan, Cambridge, MA, USA). Indeed, G.R. John (Bronx, NY, USA) has used microarrays to show that the Notch ligand Jagged 1 (important during neuronal development) is re-expressed under inflammatory conditions in the adult human CNS and might contribute to the inhibitory properties of the astrocytic scar. G. Martino (Milan, Italy) suggested that the injection of nonreplicative viral vectors into the CSF will be an effective means of delivering therapeutic gene sequences to the CNS (Ref. 3). Infected leptomeningeal and ependymal cells secrete the therapeutic protein into the CNS, avoiding the problem of the BBB and effects on the peripheral immune system resulting from systemic administration of proteins. Can Abs be used to change the immune system's perception of Ag to generate tolerance (H. Waldmann, Oxford, UK)? Regimes based on the administration of therapeutic Abs can only be used short term before they induce a humoral immune response against the therapeutic Ab (e.g. Grave's disease resulting from Ab treatment of MS patients). Even so-called 'humanized' Abs are not fully human because, by necessity, the complementarity-determining regions must remain foreign. Stealth Abs can eliminate immunogenicity (H. Waldmann); the presence of a mimitope in the Ab-binding site prevents cell binding and generates tolerance. Over time, the mimitope is released (or cleaved) and the Ab becomes available for therapy.

However, it remains far from clear whether particular immune responses are protective or destructive. If effective therapy for these devastating disorders is ever to be a clinical reality, researchers must first discover whether responses, such as inflammation, are a cause or result of disease. If inflammation is a result of disease, does it worsen the disease process or mediate a repair strategy? The substantial progress made in delineating the numerous effector cells and molecules involved in disease states must now be supported by placing these effectors into a comprehensive overview of timing and relevance. To prove that a particular cell type is present or active in a lesion is not to prove that it is an appropriate therapeutic target. Indeed, if, as some suggested, inflammation is a beneficial response, classical therapies aimed at reducing inflammation might exacerbate the disease process.

A strategy for the immunotherapy of Alzheimer's disease, using immunization with β-amyloid, has just completed Phase I trials (D. Schenk). This represents a real alternative to the pharmacological inhibition of amyloid production by β- and γ-secretase. Could therapeutic immunization be used to treat other forms of neurodegeneration caused by extracellular plaques, such as prion disease (A. Aguzzi, Zurich, Switzerland)? M. Schwartz (Rehovot, Israel) presented interesting data suggesting that autoimmunity might be protective in CNS trauma, because MBP-specific T cells can rescue neurons from secondary degeneration. T cells can also protect against glutamate toxicity.

In conclusion, therefore, researchers must establish what is harmful and what is protective, but, once appropriate targets have been identified, several therapeutic protocols have already proven their effectiveness in animal models and early clinical trials. The data presented at the conference suggest that future therapies will extend far beyond the traditional use of anti-inflammatories.

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