



Review

The Role of Dendritic Cells in Neurodegenerative Diseases

PABLO IRIBARREN*, YOU-HONG CUI, YINGYING LE and JI MING WANG

Laboratory of Molecular Immunoregulation, Center for Cancer Research, National Cancer Institute at Frederick, Frederick, MD 21702, USA

Abstract. Dendritic cells (DCs) are the most potent antigen-presenting cells (APCs) involved in the induction of adaptive immune responses. The presence of DCs in the central nervous system (CNS) and the active participation of the immune system in a variety of neurodegenerative diseases have been demonstrated. This review will discuss recent findings pertinent to DCs and other antigen-presenting cells in the CNS in health and disease states.

Key words: dendritic cells; neurodegenerative diseases; CNS.

Introduction

Evolutionary pressure has led to the development of adaptive immunity in vertebrate species. This highly sophisticated and potent system of host defense needs to be activated and regulated by antigen-presenting cells (APCs)^{5, 80}, which are heterogeneous and comprise several cell types, including macrophages, B lymphocytes and a variety of professional APCs, namely dendritic cells (DCs)⁸⁰. DCs are unique because they are the only APCs that are able to induce primary immune responses, thus resulting in the activation of naive immune cells and permitting the establishment of immunological memory^{38, 49}. DC progenitors in the bone marrow give rise to circulating precursors that home to tissues, where they reside as immature DCs (iDCs) with high phagocytic capacity²⁵. Particulated antigens, cell debris or microbes can be taken-up by iDCs through phagocytosis⁴², and enclosed in macro-pinocytic

vesicles containing extracellular fluid and solutes⁷⁰. In addition to typical cell surface markers, iDCs also express C-type lectin receptors as well as Fc γ and Fc ϵ which are crucial for antigen (Ag) uptake^{42, 43, 71}. Macro-pinocytosis and receptor-mediated Ag uptake by iDC is so efficient that picomolar and nanomolar concentrations of Ag are sufficient for antigen processing and presentation⁷². This is in sharp contrast to other types of APCs, which typically require micromolar levels of antigens.

Following Ag capture at inflammatory sites, iDCs differentiate in response to inflammatory stimuli into mature state (mDCs) and migrate to the lymphoid organs, where they interact with Ag-specific T cells and initiate immune responses^{69, 79}. Numerous factors can induce DC maturation, including exogenous pathogen-related molecules, such as lipopolysaccharide (LPS)⁶⁸, bacterial DNA³⁹, and double-stranded RNA¹⁶; endogenous host-derived pro- and anti-inflammatory signals in

The content of this publication does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government. The publisher or recipient acknowledges the right of the U.S. Government to retain a nonexclusive, royalty-free license in and to any copyright covering the article.

* Correspondence to: Pablo Iribarren, Laboratory of Molecular Immunoregulation, Center for Cancer Research, National Cancer Institute at Frederick, Building 560, Room 31-40, Frederick, MD 21702, USA, tel.: +1 301 846 5455, fax: +1 301 846 7042, e-mail: iribarrenp@mail.ncifcrf.gov

the local microenvironment, including TNF, IL-1, IL-6, IL-10, TGF- β , and prostaglandins^{5, 40}; and T cell-derived signals¹⁵.

Migration of DCs involves differential regulation of chemoattractant receptors on the cell surface during the cell maturation process⁷³. For DCs derived from peripheral blood monocytes, there is a “switch” in the pattern of chemoattractant receptor expression, which occurs at both the transcriptional and post-transcriptional levels^{78, 90}. Immature DCs express many chemokine receptors, such as CXCR1, CCR1, CCR2, CCR5 and CCR6, as well as the receptors for the classical chemoattractants, such as N-formyl-methionyl-leucyl-phenylalanine (fMLF) and C5a^{23, 79, 91}. Immediately after exposure to maturation signals, the majority of the chemokine receptors CCR1, CCR5 and CCR6 on iDCs are down-regulated from the cell surface by internalization⁷⁴. Maturing DCs express high levels of the chemokine receptor CCR7, which is essential for cell migration through lymphatics to the T cell zone of the draining lymph nodes, where the cognate CCR7 ligands CCL19/ELC and CCL21/SLC are constitutively produced³⁶. Mature DCs also upregulated the expression of CCR4 and CXCR4²⁰, but the physiological significance of these receptors in DC trafficking is less clear.

In peripheral tissues and organs where a lymphatic drainage system is present, the paradigm of chemokine-directed DC trafficking has become widely accepted. However, since such a system is apparently absent in the CNS, the process of DC differentiation, trafficking and Ag presentation in this unique anatomic compartment has become the focus of investigation by many laboratories. This review aims at discussing some recent progress in the studies of DCs in patho-physiologic states of the central nervous system (CNS).

Antigen-Presenting Cells in the CNS

The CNS was thought to be isolated from the immune system by the blood-brain barrier (BBB) and the apparent absence of a lymphatic system. The BBB only allows molecules below a certain size to pass freely from the circulation across the vascular endothelium into the CNS. The tight junctions between endothelial cells prevent the diffusion of proteins and other charged molecules into the intercellular space⁶⁶. The BBB was considered to be a barrier not only for solutes, but also for cells. However, it is now clear that the BBB does not completely isolate the CNS from the peripheral immune system, and leukocytes manage to penetrate an intact BBB and reside in the CNS². In the past, the lack

of lymphatic drainage and MHC antigen expression have been considered as contributing factors to the immune-privileged status of the CNS. For instance, the prolonged survival rate of tissue transplants in the CNS suggests the inability of the host to mount a rejection response, which involves participation of immune cells. However, accumulating evidence suggests that the normal CNS does contain cells which express MHC antigens, that lymphatic drainage occurs via the Virchow-Robin spaces, and that tissues allotransplanted into the CNS are subjected to immunological rejection, albeit at a slower rate than in other anatomical compartments². Additional evidence to support the occurrence of active immunological responses in the CNS is based on data showing that CNS fluids and intracerebrally injected antigens drain into cervical lymph nodes along perivascular pathways in the meninges and brain parenchyma⁸⁶. The perivascular spaces surrounding cerebral and meningeal blood vessels contain macrophages (the perivascular cells) which are thought to play an important role as first-line CNS scavengers and APCs^{34, 86}. Perivascular cells exhibit both constitutive and inflammation-upregulated expression of MHC class II and costimulatory molecules²². However, their capacity to travel to regional lymph nodes along perivascular spaces and to prime T cells has yet to be determined. Perivascular cells are slowly, but continuously, replaced by blood-derived cells of the monocyte/macrophage lineage⁵⁰. Since monocyte precursors can also differentiate into DCs, it is possible that some of the cells trafficking through the perivascular space may have acquired DC-like properties under the influence of inflammatory stimuli in the periphery.

Microglial cells

Although it has long been established that glia exhibit important supportive functions within the CNS, increased attention has recently been paid to the potential role of these cells in inflammation and immune responses. Astroglial cells are the predominant cell type in the CNS, while microglia and oligodendrocytes only account for a minor proportion of the cells (approximately 10 and 5%, respectively)¹⁷. In early studies, DEL RIO HORTEGA²¹ described microglia as being ubiquitous with minimal regional variations in the CNS. This assumption was later proved incomplete, and the distribution of microglia is in fact heterogeneous. A large number of microglial cells are located in close vicinity to neurons in the gray matter and between fiber tracts in the white matter of the CNS⁵¹. There are more than 5 times as many microglial cells in the gray matter than

in the white matter²¹. Interestingly, microglia are regularly distributed within a structure, with each cell occupying its own territory. Attempts to manipulate the density of the microglia in the retina failed to disrupt the regularity of the array of cell distribution⁶¹.

The origin of ramified microglia has been a long-standing controversial issue²⁶. Bone marrow-derived precursors which are of mesodermal origin, and neuroectodermal matrix cells, which also serve as precursors, for astrocytes and oligodendrocytes, both have been considered as potential sources of developing microglia. However, microglia do share most surface molecules with bone marrow-derived macrophages³⁰, making a distinction between these two cell types in pathological settings difficult. With the development of more specific immunocytochemical techniques, microglia can unequivocally be distinguished from other resident, non-neuronal cells in the CNS. Resting microglia constitutively express complement receptor (CR3, also termed Mac-1 or CD11b/CD18), which is similarly found on peripheral blood monocytes and can be further upregulated upon activation⁶⁷.

In general, resting microglia show a low-level expression of the cell surface molecules CD14, CD80 (B7-1) and HLA-DR⁷. This property has been speculated to represent an adaptation of the microglia to the specialized microenvironment of the CNS. However, the ability of microglia to respond rapidly to a variety of stimulatory molecules suggests that their apparent quiescent state does not obscure their vigilance to changes in the surrounding extracellular milieu. Necrotic brain lesions induce prompt inflammatory responses associated with the activation of microglia at the edges of the lesions and are accompanied by infiltration of hematogenous macrophages within hours after injury³¹. The activated microglia proliferate locally and reach a maximal cell expansion at day 2–3. These cells are able to rapidly phagocytose and clear debris, and produce the proinflammatory cytokine IL-1, which further stimulates microgliosis and neovascularization^{3, 32}. The most commonly described changes in activated microglia are altered cell morphology and up-regulation of constitutively expressed cell surface CR3 (Mac-1, CD11b/CD18)³⁵. A significantly enhanced expression of MHC class II molecules is observed within the first 7 days post-injury. The expression of a variety of chemoattractant receptors, which mediate migration of microglial cells, is also induced by inflammatory and immunological signals. For instance, the Gram-negative bacterial endotoxin LPS upregulates the expression of formyl peptide receptor 2 (FPR2), a homolog of human formyl peptide receptor-like 1 (FPRL1) on

murine microglia. This is a functional receptor for a great variety of chemotactic agonists, including the bacterial formylated peptide fMLF, the HIV-1 envelope protein-derived chemotactic peptides, as well as the 42-amino-acid form of amyloid β ($A\beta_{42}$) peptide, a key pathogenic agent of Alzheimer's disease⁵². LPS concomitantly downregulates murine microglial expression of CXCR4, a receptor for the chemokine SDF-1 α , which is involved in hematopoiesis and development¹⁹. Therefore, LPS, by selectively upregulating the expression and function of the formyl peptide receptor, may promote a more specialized microglial response to exogenous and endogenously produced chemoattractants.

In response to inflammatory stimulants, including LPS, microglia produce TNF- α , which in turn further activates microglia to secrete pro-inflammatory cytokines and neurotoxic mediators, including nitric oxide (NO)¹⁷. A pivotal indicator of microglia as sensors of insult in the CNS is reflected by the early nuclear induction of two active DNA-binding subunits of NF- κ B, p50 and p65, in disease models⁴⁴. For instance, in mouse experimental allergic encephalomyelitis (EAE), 4 days after transfer of encephalitogenic T cells, p50 and p65 are detected in activated microglia but not in astrocytes. Thus, microglia play a central role in mediating pro-inflammatory and immune responses in the CNS.

Dendritic cells

Initially, due to the low levels of detectable MHC class II molecules, it was believed that DCs might be absent from the CNS. However, using the monoclonal antibody OX62, which specifically reacts with an integrin only expressed in rat DCs, a small number of DCs have been identified in the meninges and stroma of the choroid plexus of rat brain¹⁰. Microglia, obtained from newborn rodent or adult human and expanded *in vitro* in the presence of astrocytes (mixed glial culture), exhibit a clear-cut macrophage phenotype and resemble ameboid, phagocytic microglia in the developing or injured CNS²⁸. However, when granulocyte macrophage colony-stimulating factor (GM-CSF) is added to the culture, microglial cells dramatically expand in number and express the typical DC surface markers Dec-205 and CD11c²⁸. In contrast, incubation with macrophage colony-stimulating factor (M-CSF) skews the microglial population toward a more defined macrophage phenotype, expressing high levels of CD11b and low levels of CD11c¹. Interestingly, SANTAMBROGIO et al.⁷⁵ suggested that brain-resident microglia, in contrast to

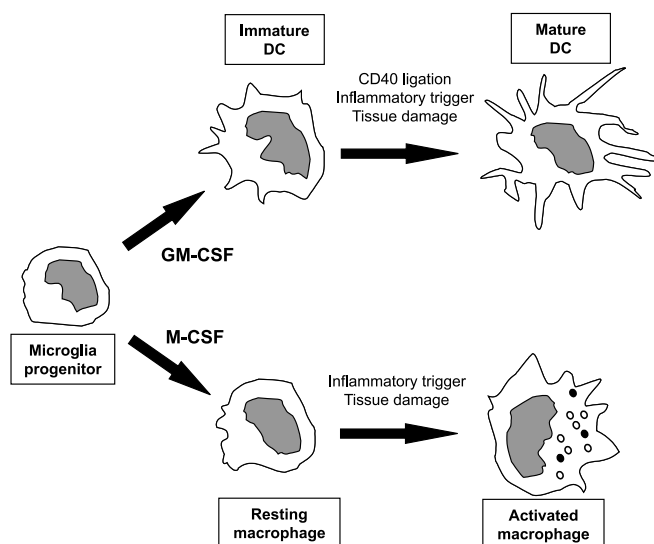


Fig. 1. Putative differentiation of antigen-presenting cells in CNS. Resident microglial cells can be skewed toward immature DC-like or macrophage-like phenotype by GM-CSF or M-CSF, respectively. Full maturation of DCs in the CNS can be promoted by environmental stimulation during inflammation, infection and tissue damage

resident macrophages in other tissues, are not terminally differentiated along the myeloid lineage. Instead, they remain in a primitive stage and may be defined as prodendritic cells, which can be skewed toward immature DC-like, or macrophage-like phenotype by using GM-CSF or M-CSF, respectively^{28, 84} (Fig. 1). In addition, the findings that neonatal microglia from primary cultures expressed cathepsins S and L, but not F, support the hypothesis that these cells more closely resemble immature DCs, but not the resident tissue macrophages found in other anatomic sites, for example within the alveolar and peritoneal spaces⁷⁵. Furthermore, brains of BALB/c mice with chronic latent toxoplasmic encephalitis also contain substantial numbers of DCs which seem to be phenotypically related to microglia²⁸. Thus, although under resting conditions DCs are present in the CNS in small numbers, they may undergo rapid expansion under pathologic conditions, probably through differentiation from microglia.

Dendritic Cells in Experimental Allergic Encephalomyelitis and Multiple Sclerosis

Multiple sclerosis (MS) is a chronic, demyelinating disease affecting the white matter of the CNS. The etiology of MS is unknown, but several lines of evidence support the hypothesis that the pathogenesis is mediated by autoreactive T lymphocytes⁸¹. Regardless of its cause, it is clear that the progression of this demyeli-

nating disease is associated with an inflammatory reaction that involves activated lymphocytes, macrophages, and endogenous glial cells (astrocytes and microglia) in the brain⁶⁴. At early stages of inflammation, the disease involves the adhesion and transmigration of leukocytes across the BBB into the CNS, which is correlated with an increased expression of adhesion molecules⁶⁵.

In human MS patients, DCs generated from adherent blood mononuclear cells did not differ substantially with respect to their yield and morphology from DCs obtained from healthy subjects, except that the DCs derived from MS patients expressed higher levels of CD1a⁵⁴. In addition, patients with MS had higher levels of DCs secreting IFN- γ , TNF- α and IL-6 than healthy subjects⁵⁴, suggesting that DCs from MS patients are in a more activated state. However, the involvement of DCs in human MS has not been elucidated.

EAE is a disease model with many features similar to human MS. EAE can be reliably elicited in different rodent species by immunization with either CNS tissue or with purified components of CNS myelin, such as myelin basic protein (MBP) and proteolipid protein (PLP). Sensitized T lymphocyte lines, propagated *in vitro* and then injected intravenously, generate "adoptive-transfer EAE", giving conclusive proof of the pivotal pathogenic role of T cells.

The presence of DCs has been reported in lesions of acute EAE in Lewis rats induced by subcutaneous (s.c.) injection with MBP in Freund's complete adjuvant (FCA)⁵⁸. The presence of OX62⁺ DCs was detected in many EAE lesions in the CNS. In general, the function of DCs in EAE is associated with the initiation of immune responses, although they also participate in the effector phase of the immune responses. For instance, NO produced by DCs not only induces apoptosis of auto-reactive T cells, but also of DCs themselves, thereby disrupting continual antigen presentation during periods of remission of EAE⁸⁸. In a study by DITTEL et al.²⁴, irradiated B10. PL mice were injected s.c. with bone marrow DCs pulsed with MBP Ac1-11 peptide. One day later, the mice were injected i.v. with MBP-TCR CD4⁺ T cells isolated from the spleen of MBP-TCR transgenic mice. The antigen-pulsed DCs efficiently presented MBP Ac1-11 peptide to antigen-specific T cells and induced EAE in recipient mice.

When administered *in vivo*, DCs can present specific antigens to T cells in either immunogenic or tolerogenic fashion²⁷, depending on the route of administration, numbers of DCs administered, and the maturation state of DC⁴⁸. As observed by FISCHER and REICHMANN²⁹, functional maturation of brain DCs oc-

curs following the onset of encephalitis and these DCs seem to be differentiated from resident microglia. In brain cells from SJL mice during EAE, DCs were identified and a correlation between the number of brain DCs and the severity of the disease was evident. The concept of local expansion of DCs in CNS under inflammation is supported by the findings that DCs can be differentiated *in vitro* from resting CD11c⁺ microglial cells²⁹. It is speculated that the emergence, maturation, and prolonged activity of DCs in EAE brain contribute to chronic Th1 responses.

XIAO et al.⁸⁹ have demonstrated that DCs, upon being pulsed *in vitro* with encephalitogenic MBP peptide 68–86 (MBP 68–86) and injected s.c. back into healthy Lewis rats, transfer immune tolerance to EAE induced by immunization with MBP 68–86 and FCA. Considering the observation that MBP 68–86 peptide-pulsed DCs can induce tolerance to EAE, it is possible that vaccination of MS patients with autologous blood DCs pulsed *in vitro* with autoantigen may be beneficial for disease control. However, a major obstacle to utilizing this scheme as a general therapeutic approach lies in the lack of characterized autoantigens responsible for the human disease.

Dendritic Cells in Alzheimer's Disease

Alzheimer's disease (AD) is a progressive neurological disorder that is characterized by memory loss, disorientation and behavioral changes. There is good evidence indicating that aberrant production and accumulation of the β -amyloid (A β) peptides, the 42-amino-acid form of A β (A β ₄₂) in particular, are primary events in the pathogenesis of AD⁷⁷. As a proteolytic cleavage product of the A β precursor protein (APP)⁶⁰, both soluble and aggregated A β ₄₂ have been reported to be directly toxic to neurons⁷⁷. It has also been established that inflammatory response in the brain, mediated by A β ₄₂-activated astrocytes and microglia, plays an important role in the disease progression of AD⁵⁹. A β -activated astroglial cells elaborate pro-inflammatory cytokines, such as IL-1 β , IL-6 and TNF- α , as well as other mediators, which promote neuronal death³³. On the other hand, studies suggest that as phagocytic cells in the brain, activated microglia may also play a role in the up-take and clearance of A β peptides, thus limiting their accumulation⁹².

Since AD appears to be a degenerative disease associated with chronic inflammation and does not involve active participation of the adaptive immune system, the role of DCs in the pathological events of AD may not

be as important as in MS. Nevertheless, observations, limited up to now, have revealed some unique features of DC interaction with A β peptide. SCHMITT et al.⁷⁶ monitored the survival, cytokine release, and surface marker expression by human DCs after exposure to A β peptides. Some peptide aggregates were found in intracellular vacuoles of DCs, suggesting an active uptake of A β peptides by the cells, presumably through phagocytosis. This process did not increase the production of TNF- α and did not change the surface expression of CD18, CD11a or CD11b by DCs. However, a decrease in the surface expression of MHC class II molecules was observed. DCs pulsed with A β aggregates *in vitro* were unable to stimulate T cells in an autologous co-culture system⁷⁶. This observation suggests that amyloid peptide may escape immune recognition by inhibiting MHC class II surface expression on DCs and suppressing their capacity to act as APCs.

Interestingly, recent studies indicate that activation of an effective adaptive immune response in AD may have therapeutic potential⁸⁷. This approach has been tested in transgenic mice overexpressing human APP, which develop AD-like syndromes with A β ₄₂ deposition in the brain and dementia. Vaccination of mice with aggregated human A β ₄₂ reduced the formation of A β plaques⁹², and in older animals, vaccination resulted in a reduction in the size and the number of existing plaques. A β ₄₂-vaccinated mice exhibited significant cognitive improvement, suggesting a highly effective immunotherapy in AD-like animals. While the mechanism of plaque clearance by A β ₄₂ vaccination remains to be determined, BARD et al.⁶ reported that injection of an antibody specific to A β ₄₂ in transgenic mice initiated the clearance of antibody-bound A β aggregates in the brain by microglial cells.

It is therefore clear that in animal models of AD, vaccination with A β ₄₂ elicits a potent antibody response, which most likely requires antigen recognition and presentation by DCs in the periphery. However, whether vaccination is also suitable for human patients should be handled with caution because, as discussed earlier, treatment of human DCs with A β ₄₂ could actually reduce MHC class II expression on the cells and suppress their APC capacity.

Dendritic Cells in Prion Diseases

Prion diseases (transmissible spongiform encephalopathies, TSE) are a group of fatal progressive neurological disorders including Creutzfeldt-Jakob disease, Gerstmann-Sträussler-Scheinker syndrome and fatal

familial insomnia in humans, as well as bovine spongiform encephalopathy (BSE) and scrapie in other species. The etiological agent of these diseases is proposed to be an aberrant isoform of a cell surface glycoprotein, the prion protein (PrPc)⁶³. To maintain TSE infection, host cells must express the normal cellular isomer of the prion protein, as mice deficient in PrPc (Prnp^{-/-} mice) do not develop disease after peripheral injection of the infectious PrPc isoform^{13, 57}. Following experimental peripheral infection with scrapie, the pathologic isoform of PrPc (PrPSc) rapidly accumulates in lymphoid tissues^{8, 46, 56}, long before its appearance in the CNS. This peripheral “replication” leads to a progressive invasion of the CNS, in which PrPSc is deposited in the extracellular space of the diseased CNS infiltrated by activated astrocytes and mononuclear phagocytes (microglia)⁶². The mechanisms of PrPSc toxicity for neurons are not clear, but seem to involve activation of microglia and oxidative stress. In cell culture experiments, BROWN and KRETZSCHMAR¹¹ demonstrated that a pathogenic fragment of human PrPc, PrP₁₀₆₋₁₂₆, is toxic to cells from the cerebellum and that this toxicity requires the presence of microglia. In response to PrP₁₀₆₋₁₂₆, microglia increase their production of oxygen radicals and pro-inflammatory cytokines. LE et al.⁵³ showed that PrP₁₀₆₋₁₂₆ is chemotactic for human monocytes through the use of a G protein-coupled receptor FPRL1, which has been reported to interact with a diverse array of exogenous and endogenous ligands. Upon stimulation by PrP₁₀₆₋₁₂₆, FPRL1 underwent a rapid internalization and, furthermore, PrP₁₀₆₋₁₂₆ enhanced monocyte production of pro-inflammatory cytokines, which was inhibited by pertussis toxin⁵³. Recently, the expression of a FPRL1 homolog, FPR2, on murine microglial cells has been demonstrated¹⁹. Thus, FPRL1 in human or FPR2 in mice may provide a molecular basis for the interaction of PrP₁₀₆₋₁₂₆ with microglial cells.

TSE displays a long incubation period and, initially, the prion titer increases in peripheral lymphoid organs⁸, where follicular dendritic cells (FDCs) appear to support prion replication. Recent studies have shown that FDCs of the germinal centers of the spleen, lymph nodes and Peyer’s patches are key players in TSE pathogenesis. The normal functions of FDCs are to trap and retain native antigens in the form of immune complexes for presentation to B cells⁸³. Complement also plays an important role in the localization and retention of scrapie to FDCs during the first few days after infection⁵⁵. The classical complement activation pathway was most likely to be involved in C3 activation during scrapie infection, as the incubation period was marked-

ly prolonged in mice deficient in both classical and alternative pathways (*H2-Bf/C2*^{-/-} mice)⁸² or in mice with classical pathway deficiency (*C1qa*^{-/-} mice)^{9, 47, 55}.

High levels of PrPSc are detected on FDCs in TSE-infected mice⁸². Abnormal PrPSc accumulation is also seen within the germinal centers in Creutzfeldt-Jakob disease⁴¹ and sheep scrapie⁸⁵. It has been reported that SCID mice are much less susceptible than immunocompetent mice to peripheral challenge with TSE agents, although they are fully susceptible when infectious agents are introduced directly into their brains⁴⁵. This resistance to peripheral challenge is attributed to an inability of SCID lymphoid tissues to support PrPSc replication, which requires participation of FDCs. B cells may also be important in terms of their requirement for the maturation of FDCs. However, involvement of FDCs alone is not sufficient to explain how the infectious forms of the prion protein are transported from the gastrointestinal tract to the lymphoid organs and CNS. FDCs reside within B cell areas of lymphoid organs where they bind and retain antigens on the cell surface for months or years⁸³. These cells have a very slow turnover rate and are believed not to recirculate. Moreover, cellular PrPc has not been found to be associated with the FDCs in enteric lymphoid tissue³⁷. Therefore, some missing links within the chain of transportation of infectious PrPSc require further clarification. Interestingly, CD11c⁺ DCs, a cell type unrelated to FDCs, are able to propagate infectious prions from the periphery to the CNS in the absence of any additional lymphoid element⁴. In addition, BURTHEM et al.¹⁴ demonstrated that high levels of PrPc are present on myeloid DCs that surround the splenic white pulp. These myeloid DCs are ontologically and functionally distinct from FDCs. Consistent with these observations, expression of PrPc was strongly induced during the generation of mature myeloid DCs *in vitro*. In these cells, PrPc colocalized with MHC class II molecules. Given the close anatomic and functional connection of myeloid DCs with lymphoid follicles, it is suggested that myeloid DCs may also play a role in the propagation of PrPSc in humans.

Concluding Remarks

Although the complex interactions between the CNS and the immune system are not fully understood, accumulating evidence suggests that immune cells play important roles in the pathogenesis and progression of neurodegenerative diseases. The low frequency of DC precursors and mature DCs in the normal CNS initially

suggested that DCs might not be relevant to neurodegenerative diseases. However, under inflammatory conditions, the number of DCs increases significantly so that such cells are readily detectable and can be isolated from the CNS. Furthermore, the resident macrophages in the brain, the microglia, have the capacity to differentiate into effective APCs. While the role of DCs in antigen presentation and cross-talk with other immune cells in the CNS requires further investigation, DCs in the periphery have been shown to be pivotal in some forms of neurodegenerative diseases, in which immune responses to self antigen are the causative factors. In prion diseases, both FDCs and myeloid DCs are involved in the replication and transmission of infectious prion isoforms. In AD, although immune responses have not been implicated in the development and progression of the disease, successful vaccination in mouse models of AD suggests a novel therapeutic approach based on activation of the immune system, which surely requires antigen recognition and processing by APCs. Thus, a better understanding of DCs, or APCs in general, in neurodegenerative diseases will promote the elucidation of the pathogenic mechanisms and the development of therapeutic approaches.

Acknowledgment. The authors thank Dr. J. J. Oppenheim for reviewing the manuscript; N. Dunlop and W. Gong for technical support; and C. Fogle and C. Nolan for secretarial assistance. This project has been funded in part with Federal funds from the National Cancer Institute, National Institutes of Health, under Contract No. NO1-CO-56000. Animal care was provided in accordance with the procedures outlined in the "Guide for the Care and Use of Laboratory Animals" (NIH Publication No. 86-23, 1985).

References

- ALOISI F., RIA F. and ADORINI L. (2000): Regulation of T-cell responses by CNS antigen-presenting cells: different roles for microglia and astrocytes. *Immunol. Today*, **21**, 141–147.
- ALUN BROWN K. (2001): Factors modifying the migration of lymphocytes across the blood–brain barrier. *Int. Immunopharmacol.*, **1**, 2043–2062.
- AMAT J. A., ISHIGURO H., NAKAMURA K. and NORTON W. T. (1996): Phenotypic diversity and kinetics of proliferating microglia and astrocytes following cortical stab wounds. *Glia*, **16**, 368–382.
- AUCOUTURIER P., GEISSMANN F., DAMOTTE D., SABORIO G. P., MEEKER H. C., KASCSAK R., KASCSAK R., CARP R. I. and WISNIEWSKI T. (2001): Infected splenic dendritic cells are sufficient for prion transmission to the CNS in mouse scrapie. *J. Clin. Invest.*, **108**, 703–708.
- BANCHEREAU J. and STEINMAN R. M. (1998): Dendritic cells and the control of immunity. *Nature*, **392**, 245–252.
- BARD F., CANNON C., BARBOUR R., BURKE R. L., GAMES D., GRAJEDA H., GUIDO T., HU K., HUANG J., JOHNSON-WOOD K., KHAN K., KHOLODENKO D., LEE M., LIEBERBURG I., MOTTER R., NGUYEN M., SORIANO F., VASQUEZ N., WEISS K., WELCH B., SEUBERT P., SCHENK D. and YEDNOCK T. (2000): Peripherally administered antibodies against amyloid beta-peptide enter the central nervous system and reduce pathology in a mouse model of Alzheimer disease. *Nat. Med.*, **6**, 916–919.
- BECHER B. and ANTEL J. P. (1996): Comparison of phenotypic and functional properties of immediately *ex vivo* and cultured human adult microglia. *Glia*, **18**, 1–10.
- BEEKES M. and MCBRIDE P. A. (2000): Early accumulation of pathological PrP in the enteric nervous system and gut-associated lymphoid tissue of hamsters orally infected with scrapie. *Neurosci. Lett.*, **278**, 181–184.
- BOTTO M., DELL'AGNOLA C., BYGRAVE A. E., THOMPSON E. M., COOK H. T., PETRY F., LOOS M., PANDOLFI P. P. and WALPORT M. J. (1998): Homozygous C1q deficiency causes glomerulonephritis associated with multiple apoptotic bodies. *Nat. Genet.*, **19**, 56–59.
- BRENAN M. and REES D. J. (1997): Sequence analysis of rat integrin alpha E1 and alpha E2 subunits: tissue expression reveals phenotypic similarities between intraepithelial lymphocytes and dendritic cells in lymph. *Eur. J. Immunol.*, **27**, 3070–3079.
- BROWN D. R. and KRETZSCHMAR H. A. (1997): Microglia and prion disease: a review. *Histol. Histopathol.*, **12**, 883–892.
- BROWN K. L., STEWART K., RITCHIE D. L., MABBOTT N. A., WILLIAMS A., FRASER H., MORRISON W. I. and BRUCE M. E. (1999): Scrapie replication in lymphoid tissues depends on prion protein-expressing follicular dendritic cells. *Nat. Med.*, **5**, 1308–1312.
- BUELER H., FISCHER M., LANG Y., BLUETHMANN H., LIPP H. P., DEARMOND S. J., PRUSINER S. B., AGUET M. and WEISSMANN C. (1992): Normal development and behaviour of mice lacking the neuronal cell-surface PrP protein. *Nature*, **356**, 577–582.
- BURTHEM J., URBAN B., PAIN A. and ROBERTS D. J. (2001): The normal cellular prion protein is strongly expressed by myeloid dendritic cells. *Blood*, **98**, 3733–3738.
- CAUX C., MASSACRIER C., VANBERVLIET B., DUBOIS B., VAN KOOTEN C., DURAND I. and BANCHEREAU J. (1994): Activation of human dendritic cells through CD40 cross-linking. *J. Exp. Med.*, **180**, 1263–1272.
- CELLA M., SALIO M., SAKAKIBARA Y., LANGEN H., JULKUNEN I. and LANZAVECCHIA A. (1999): Maturation, activation, and protection of dendritic cells induced by double-stranded RNA. *J. Exp. Med.*, **189**, 821–829.
- CHAO C. C., HU S., PETERSON P. K. (1996): Glia: the not so innocent bystanders. *J. Neurovirol.*, **2**, 234–239.
- CHAO C. C., HU S., SHENG W. S., BU D., BUKRINSKY M. I. and PETERSON P. K. (1996): Cytokine-stimulated astrocytes damage human neurons via a nitric oxide mechanism. *Glia*, **16**, 276–284.
- CUI Y. H., LE Y., GONG W., PROOST P., VAN DAMME J., MURPHY W. and WANG J. M. (2002): Bacterial lipopolysaccharide selectively up-regulates the function of the chemotactic peptide receptor FPR2 in murine microglial cells. *J. Immunol.*, **168**, 434–442.
- DELGADO E., FINKEL V., BAGGIOLINI M., MACKAY C. R., STEINMAN R. M. and GRANELLI-PIPERNO A. (1998): Mature dendritic cells respond to SDF-1, but not to several beta-chemokines. *Immunobiology*, **198**, 490–500.
- DEL RIO HORTEGA P. (1932): Microglia. In: PENFIELD W.: *Cytology and cellular pathology of the nervous system*. Paul Hoeber, New York, **2**, 481–534.

22. DE SIMONE R., GIAMPAOLO A., GIOMETTO B., GALLO P., LEVI G., PESCHLE C. and ALOISI F. (1995): The costimulatory molecule B7 is expressed on human microglia in culture and in multiple sclerosis acute lesions. *J. Neuropathol. Exp. Neurol.*, **54**, 175–187.
23. DIEU M. C., VANBERVLIET B., VICARI A., BRIDON J. M., OLDHAM E., AIT-YAHIA S., BRIERE F., ZLOTNIK A., LEBECQUE S. and CAUX C. (1998): Selective recruitment of immature and mature dendritic cells by distinct chemokines expressed in different anatomic sites. *J. Exp. Med.*, **188**, 373–386.
24. DITTEL B. N., VISINTIN I., MERCHANT R. M. and JANEWAY C. A. JR. (1999): Presentation of the self antigen myelin basic protein by dendritic cells leads to experimental autoimmune encephalomyelitis. *J. Immunol.*, **163**, 32–39.
25. FEARNLEY D. B., WHYTE L. F., CARNOUTSOS S. A., COOK A. H., HART D. N. (1999): Monitoring human blood dendritic cell numbers in normal individuals and in stem cell transplantation. *Blood*, **93**, 728–736.
26. FEDOROFF S., ZHAI R. and NOVAK J. P. (1997): Microglia and astroglia have a common progenitor cell. *J. Neurosci. Res.*, **50**, 477–486.
27. FINKELMAN F. D., LEES A., BIRNBAUM R., GAUSE W. C. and MORRIS S. C. (1996): Dendritic cells can present antigen *in vivo* in a tolerogenic or immunogenic fashion. *J. Immunol.*, **157**, 1406–1414.
28. FISCHER H. G., BONIFAS U. and REICHMANN G. (2000): Phenotype and functions of brain dendritic cells emerging during chronic infection of mice with *Toxoplasma gondii*. *J. Immunol.*, **164**, 4826–4834.
29. FISCHER H. G. and REICHMANN G. (2001): Brain dendritic cells and macrophages/microglia in central nervous system inflammation. *J. Immunol.*, **166**, 2717–2726.
30. FLARIS N. A., DENSMORE T. L., MOLLESTON M. C. and HICKEY W. F. (1993): Characterization of microglia and macrophages in the central nervous system of rats: definition of the differential expression of molecules using standard and novel monoclonal antibodies in normal CNS and in four models of parenchymal reaction. *Glia*, **7**, 34–40.
31. GIULIAN D., CHEN J., INGEMAN J. E., GEORGE J. K. and NOPONEN M. (1989): The role of mononuclear phagocytes in wound healing after traumatic injury to adult mammalian brain. *J. Neurosci.*, **9**, 4416–4429.
32. GIULIAN D., WOODWARD J., YOUNG D. G., KREBS J. F. and LACHMAN L. B. (1988): Interleukin-1 injected into mammalian brain stimulates astrogliosis and neovascularization. *J. Neurosci.*, **8**, 2485–2490.
33. GONZALEZ-SCARANO F. and BALTUCH G. (1999): Microglia as mediators of inflammatory and degenerative diseases. *Annu. Rev. Neurosci.*, **22**, 219–240.
34. GRAEBER M. B., STREIT W. J., BURINGER D., SPARKS D. L. and KREUTZBERG G. W. (1992): Ultrastructural location of major histocompatibility complex (MHC) class II perivascular cells in histologically normal human brain. *J. Neuropathol. Exp. Neurol.*, **51**, 303–311.
35. GRAEBER M. B., STREIT W. J., KREUTZBERG G. W. (1988): Axotomy of the rat facial nerve leads to increased CR3 complement receptor expression by activated microglial cells. *J. Neurosci. Res.*, **21**, 18–24.
36. GUNN M. D., KYUWA S., TAM C., KAKIUCHI T., MATSUZAWA A., WILLIAMS L. T. and NAKANO H. (1999): Mice lacking expression of secondary lymphoid organ chemokine have defects in lymphocyte homing and dendritic cell localization. *J. Exp. Med.*, **189**, 451–460.
37. HAINFELLNER J. A. and BUDKA H. (1999): Disease associated prion protein may deposit in the peripheral nervous system in human transmissible spongiform encephalopathies. *Acta Neuropathol.*, **98**, 458–460.
38. HART D. N. (1997): Dendritic cells: unique leukocyte populations which control the primary immune response. *Blood*, **90**, 3245–3287.
39. HARTMANN G., WEINER G. J. and KRIEG A. M. (1999): CpG DNA: a potent signal for growth, activation, and maturation of human dendritic cells. *Proc. Natl. Acad. Sci. USA*, **96**, 9305–9310.
40. HEUFLE C., KOCH F. and SCHULER G. (1988): Granulocyte/macrophage colony-stimulating factor and interleukin-1 mediate the maturation of murine epidermal Langerhans cells into potent immunostimulatory dendritic cells. *J. Exp. Med.*, **167**, 700–705.
41. HILL A. F., BUTTERWORTH R. J., JOINER S., JACKSON G., ROSSOR M. N., THOMAS D. J., FROSH A., TOLLEY N., BELL J. E., SPENCER M., KING A., AL-SARRAJ S., IRONSIDE J. W., LANTOS P. L. and COLLINGE J. (1999): Investigation of variant Creutzfeldt-Jakob disease and other human prion diseases with tonsil biopsy samples. *Lancet*, **353**, 183–189.
42. INABA K., INABA M., NAITO M. and STEINMAN R. M. (1993): Dendritic cell progenitors phagocytose particulates, including bacillus Calmette-Guerin organisms, and sensitize mice to mycobacterial antigens *in vivo*. *J. Exp. Med.*, **178**, 479–488.
43. JIANG W., SWIGGARD W. J., HEUFLE C., PENG M., MIRZA A., STEINMAN R. M. and NUSSENZWEIG M. C. (1995): The receptor DEC-205 expressed by dendritic cells and thymic epithelial cells is involved in antigen processing. *Nature*, **375**, 151–155.
44. KALTSCHMIDT C., KALTSCHMIDT B., LANNES-VIEIRA J., KREUTZBERG G. W., WEKERLE H., BAEUERLE P. A. and GEHRMANN J. (1994): Transcription factor NF- κ B is activated in microglia during experimental autoimmune encephalomyelitis. *J. Neuroimmunol.*, **55**, 99–106.
45. KAPASI Z. F., BURTON G. F., SHULTZ L. D., TEW J. G. and SZAKAL A. K. (1993): Induction of functional follicular dendritic cell development in severe combined immunodeficiency mice. Influence of B and T cells. *J. Immunol.*, **150**, 2648–2658.
46. KIMBERLIN R. H. and WALKER C. A. (1979): Pathogenesis of mouse scrapie: dynamics of agent replication in spleen, spinal cord and brain after infection by different routes. *J. Comp. Pathol.*, **89**, 551–562.
47. KLEIN M. A., KAESER P. S., SCHWARZ P., WEYD H., XENARIOS I., ZINKERNAGEL R. M., CARROLL M. C., VERBEEK J. S., BOTTO M., WALPORT M. J., MOLINA H., KALINKE U., ACHA-ORBEA H. and AGUZZI A. (2001): Complement facilitates early prion pathogenesis. *Nat. Med.*, **7**, 488–492.
48. LABEUR M. S., ROTERS B., PERS B., MEHLING A., LUGER T. A., SCHWARZ T. and GRABBE S. (1999): Generation of tumor immunity by bone marrow-derived dendritic cells correlates with dendritic cell maturation stage. *J. Immunol.*, **162**, 168–175.
49. LANZAVECCHIA A. and SALLUSTO F. (2001): The instructive role of dendritic cells on T cell responses: lineages, plasticity and kinetics. *Curr. Opin. Immunol.*, **13**, 291–298.
50. LASSMANN H., SCHMIED M., VASS K., HICKEY W. F. (1993): Bone marrow derived elements and microglia in brain inflammation. *Glia*, **7**, 19–24.
51. LAWSON L. J., PERRY V. H., DRI P. and GORDON S. (1990):

- Heterogeneity in the distribution and morphology of microglia in the normal adult mouse brain. *Neuroscience*, **39**, 151–170.
52. LE Y., OPPENHEIM J. J. and WANG J. M. (2001): Pleiotropic roles of formyl peptide receptors. *Cytokine Growth Factor Rev.*, **12**, 91–105.
 53. LE Y., YAZAWA H., GONG W., YU Z., FERRANS V. J., MURPHY P. M. and WANG J. M. (2001): The neurotoxic prion peptide fragment PrP(106–126) is a chemotactic agonist for the G protein-coupled receptor formyl peptide receptor-like 1. *J. Immunol.*, **166**, 1448–1451.
 54. LINK H., HUANG Y. M., MASTERMAN T. and XIAO B. G. (2001): Vaccination with autologous dendritic cells: from experimental autoimmune encephalomyelitis to multiple sclerosis. *J. Neuroimmunol.*, **114**, 1–7.
 55. MABBOTT N. A., BRUCE M. E., BOTTO M., WALPORT M. J. and PEPYS M. B. (2001): Temporary depletion of complement component C3 or genetic deficiency of C1q significantly delays onset of scrapie. *Nat. Med.*, **7**, 485–487.
 56. MABBOTT N. A., WILLIAMS A., FARQUHAR C. F., PASPARAKIS M., KOLLIAS G. and BRUCE M. E. (2000): Tumor necrosis factor α -deficient, but not interleukin-6-deficient, mice resist peripheral infection with scrapie. *J. Virol.*, **74**, 3338–3344.
 57. MANSON J. C., CLARKE A. R., HOOPER M. L., AITCHISON L., MCCONNELL I. and HOPE J. (1994): 129/Ola mice carrying a null mutation in PrP that abolishes mRNA production are developmentally normal. *Mol. Neurobiol.*, **8**, 121–127.
 58. MATYSZAK M. K. and PERRY V. H. (1996): The potential role of dendritic cells in immune-mediated inflammatory diseases in the central nervous system. *Neuroscience*, **74**, 599–608.
 59. MCGEER E. G. and MCGEER P. L. (1998): The importance of inflammatory mechanisms in Alzheimer disease. *Exp. Gerontol.*, **33**, 371–378.
 60. NUNAN J. and SMALL D. H. (2000): Regulation of APP cleavage by α -, β - and γ -secretases. *FEBS Lett.*, **483**, 6–10.
 61. PERRY V. H. (1994): Macrophages and the nervous system. Landes R. G. Company, Austin, 6–27.
 62. PERRY V. H., BOLTON S. J., ANTHONY D. C., and BETMOUNI S. (1998): The contribution of inflammation to acute and chronic neurodegeneration. *Res. Immunol.*, **149**, 721–725.
 63. PRUSINER S. B. (1998): Prions. *Proc. Natl. Acad. Sci. USA*, **95**, 13363–13383.
 64. RAINE C. S. (1994): The Dale E. McFarlin memorial lecture: the immunology of the multiple sclerosis lesion. *Ann. Neurol.*, **36**, 61–72.
 65. RAINE C. S. and CANNELLA B. (1992): Adhesion molecules and central nervous system inflammation. *Semin. Neurosci.*, **4**, 201–211.
 66. REESE T. S. and KARNOVSKY M. J. (1967): Fine structural localization of a blood-brain barrier to exogenous peroxidase. *J. Cell. Biol.*, **34**, 207–217.
 67. REID D. M., PERRY V. H., ANDERSSON P. B. and GORDON S. (1993): Mitosis and apoptosis of microglia *in vivo* induced by an anti-CR3 antibody which crosses the blood-brain barrier. *Neuroscience*, **56**, 529–533.
 68. RESCIGNO M., GRANUCCI F., CITTERIO S., FOTI M., and RICCIARDI-CASTAGNOLI P. (1999): Coordinated events during bacteria-induced DC maturation. *Immunol. Today*, **20**, 200–203.
 69. ROAKE J. A., RAO A. S., MORRIS P. J., LARSEN C. P., HANKINS D. F., AUSTYN J. M. (1995): Dendritic cell loss from nonlymphoid tissues after systemic administration of lipopolysaccharide, tumor necrosis factor, and interleukin 1. *J. Exp. Med.*, **181**, 2237–2247.
 70. SALLUSTO F., CELLA M., DANIELI C. and LANZAVECCHIA A. (1995): Dendritic cells use macropinocytosis and the mannose receptor to concentrate macromolecules in the major histocompatibility complex class II compartment: downregulation by cytokines and bacterial products. *J. Exp. Med.*, **182**, 389–400.
 71. SALLUSTO F. and LANZAVECCHIA A. (1994): Efficient presentation of soluble antigen by cultured human dendritic cells is maintained by granulocyte/macrophage colony-stimulating factor plus interleukin 4 and downregulated by tumor necrosis factor α . *J. Exp. Med.*, **179**, 1109–1118.
 72. SALLUSTO F. and LANZAVECCHIA A. (1995): Dendritic cells use macropinocytosis and the mannose receptor to concentrate antigen to the MHC class II compartment. Downregulation by cytokines and bacterial products. *J. Exp. Med.*, **182**, 389–400.
 73. SALLUSTO F. and LANZAVECCHIA A. (2000): Understanding dendritic cell and T-lymphocyte traffic through the analysis of chemokine receptor expression. *Immunol. Rev.*, **177**, 134–140.
 74. SALLUSTO F., PALERMO B., LENIG D., MIETTINEN M., MATTIKAINEN S., JULKUNEN I., FORSTER R., BURGSTALLER R., LIPP M. and LANZAVECCHIA A. (1999): Distinct patterns and kinetics of chemokine production regulate dendritic cell function. *Eur. J. Immunol.*, **29**, 1617–1625.
 75. SANTAMBROGIO L., BELYANSKAYA S. L., FISCHER F. R., CIPRIANI B., BROSNAN C. F., RICCIARDI-CASTAGNOLI P., STERN L. J., STROMINGER J. L. and RIESE R. (2001): Developmental plasticity of CNS microglia. *Proc. Natl. Acad. Sci. USA*, **98**, 6295–6300.
 76. SCHMITT T. L., STEGER M. M., PAVELKA M. and GRUBECK-LOEBENSTEIN B. (1997): Interactions of the Alzheimer beta amyloid fragment (25–35) with peripheral blood dendritic cells. *Mech. Ageing Dev.*, **94**, 223–232.
 77. SMALL D. H. and MCLEAN C. A. (1999): Alzheimer's disease and the amyloid beta protein: What is the role of amyloid? *J. Neurochem.*, **73**, 443–449.
 78. SOZZANI S., ALLAVENA P., D'AMICO G., LUINI W., BIANCHI G., KATAURA M., IMAI T., YOSHIE O., BONECCHI R. and MANTOVANI A. (1998): Differential regulation of chemokine receptors during dendritic cell maturation: a model for their trafficking properties. *J. Immunol.*, **161**, 1083–1086.
 79. SOZZANI S., SALLUSTO F., LUINI W., ZHOU D., PIEMONTE L., ALLAVENA P., VAN DAMME J., VALITUTTI S., LANZAVECCHIA A. and MANTOVANI A. (1995): Migration of dendritic cells in response to formyl peptides, C5a, and a distinct set of chemokines. *J. Immunol.*, **155**, 3292–3295.
 80. SPRENT J. (1995): Antigen-presenting cells. Professionals and amateurs. *Curr. Biol.*, **5**, 1095–1097.
 81. STEINMAN L. (1996): Multiple sclerosis: a coordinated immunological attack against myelin in the central nervous system. *Cell*, **85**, 299–302.
 82. TAYLOR P. R., NASH J. T., THEODORIDIS E., BYGRAVE A. E., WALPORT M. J. and BOTTO M. (1998): A targeted disruption of the murine complement factor B gene resulting in loss of expression of three genes in close proximity, factor B, C2, and D17H6S45. *J. Biol. Chem.*, **273**, 1699–1704.
 83. TEW J. G., WU J., FAKHER M., SZAKAL A. K. and QIN D. (2001): Follicular dendritic cells: beyond the necessity of T-cell help. *Trends Immunol.*, **22**, 361–367.
 84. ULVESTAD E., WILLIAMS K., BJERKVIG R., TIEKOTTER K., ANTEL J. and MATRE R. (1994): Human microglial cells have phenotypic and functional characteristics in common with both

- macrophages and dendritic antigen-presenting cells. *J. Leukoc. Biol.*, **56**, 732–740.
85. VAN KEULEN L. J., SCHREUDER B. E., MELOEN R. H., MOOIJ-HARKES G., VROMANS M. E. and LANGEVELD J. P. (1996): Immunohistochemical detection of prion protein in lymphoid tissues of sheep with natural scrapie. *J. Clin. Microbiol.*, **34**, 1228–1231.
 86. WELLER R. O. (1998): Pathology of cerebrospinal fluid and interstitial fluid of the CNS: significance for Alzheimer disease, prion disorders and multiple sclerosis. *J. Neuropathol. Exp. Neurol.*, **57**, 885–894.
 87. WENINGER S. C. and YANKNER B. A. (2001): Inflammation and Alzheimer disease: the good, the bad, and the ugly. *Nat. Med.*, **7**, 527–528.
 88. XIAO B. G., HUANG Y. M., XU L. Y., ISHIKAWA M. and LINK H. (1999): Mechanisms of recovery from experimental allergic encephalomyelitis induced with myelin basic protein peptide 68–86 in Lewis rats: a role for dendritic cells in inducing apoptosis of CD4⁺ T cells. *J. Neuroimmunol.*, **97**, 25–36.
 89. XIAO B. G., HUANG Y. M., YANG J. S., XU L. Y. and LINK H. (2001): Bone marrow-derived dendritic cells from experimental allergic encephalomyelitis induce immune tolerance to EAE in Lewis rats. *Clin. Exp. Immunol.*, **125**, 300–309.
 90. YANG D., CHEN Q., LE Y., WANG J. M. and OPPENHEIM J. J. (2001): Differential regulation of formyl peptide receptor-like 1 expression during the differentiation of monocytes to dendritic cells and macrophages. *J. Immunol.*, **166**, 4092–4098.
 91. YANG D., HOWARD O. M., CHEN Q. and OPPENHEIM J. J. (1999): Cutting edge: immature dendritic cells generated from monocytes in the presence of TGF- β 1 express functional C-C chemokine receptor 6. *J. Immunol.*, **163**, 1737–1741.
 92. YANKNER B. A. (1996): Mechanisms of neuronal degeneration in Alzheimer's disease. *Neuron.*, **16**, 921–932.

Received in January 2002

Accepted in March 2002