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An introduction to neuroimmunology

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Classically the brain has been regarded as an ‘immunologically privileged’ site, because alien tissue grafts transplanted there survive longer than similar grafts in other sites (Barker & Billingham, 1977). The relative hospitality of the brain to foreign tissue has been attributed to a lack of lymphatic drainage, the presence of the blood–brain barrier, the lack of constitutive expression of major histocompatibility complex (MHC) molecules, and the possible presence of chemical substances that might inhibit lymphocyte traffic. However, recent studies indicate that, in general, immune responses proceed in the nervous system in a similar manner to that in other organs. Yet the nervous system still has a number of attributes that influence local immune responses and that may be relevant to the pathogenesis of autoimmune neurological disease.

Specialization of structure and function in the nervous system

Central and peripheral nervous system

The nervous system is subdivided into the central nervous system (CNS) and the peripheral nervous system (PNS). The CNS comprises the cerebral hemispheres, the cerebellum, the brainstem, the spinal cord, and the olfactory and optic nerves. The PNS comprises the cranial nerve roots and cranial nerves, the spinal nerve roots (dorsal and ventral), the dorsal root ganglia, the spinal nerves and the peripheral nerves. The junctions of the CNS and PNS are defined by transitional zones where the dorsal roots enter the spinal cord (dorsal root entry zones) and where the ventral roots exit from the spinal cord (ventral root exit zones) and where the third to twelfth cranial nerves enter or leave the brainstem. The autonomic nervous system

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is a functional subdivision of both the CNS and

Cellular components

The CNS is comprised of neuronal populations that express different functions. Specialized populations of cells with different functions are also present. The glial population comprises astrocytes, oligodendrocytes and microglia. The frontal zone is by the spiral compo...

Diversity of potential autoimmunity neurons

As a consequence of the presence of autoantigens and clinical observations, a neuroimmunology in the case of autoimmune disease, as in the myelin sheath disease, is relevant because of the segmentation of the system.

The blood–brain interface

The blood–brain barrier is formed by the administered dyes such as as a tracer. Reese's glycoprotein, located at the level of the perivascular immunological junctions. Other elements of the perivascular g...
is a functional subdivision of the nervous system which has components in both the CNS and the PNS.

**Cellular components and subcellular specialization**

The CNS is composed of neurones, glia, blood vessels and meninges. The neuronal population consists of subsets of highly specialized cells which express different cytoplasmic and cell surface proteins and which have different functions. Furthermore, the individual neurones exhibit subcellular specialization with dendritic, somatic, axonal and synaptic regions. The glial population consists of cells with a neuroectodermal origin (astrocytes, oligodendrocytes and ependymal cells) and cells that are derived from bone marrow (microglia). Oligodendrocytes form myelin sheaths around axons by the spiral compaction of their plasma membranes. The PNS is mainly composed of axons, Schwann cells (which form the myelin sheaths) and connective tissue elements. In the dorsal root ganglion region, neuronal cell bodies are also present.

**Diversity of potential target antigens and clinical syndromes in autoimmune neurological disease**

As a consequence of the diversity of specialized cells and subcellular components in the nervous system, there is a wide range of potential target antigens and clinical syndromes in autoimmune neurological disease. Even in the case of autoimmunity directed at a single specialized structure, such as the myelin sheath, there may be a wide range of clinical presentations, because of the segmental and topographical organization of the nervous system.

**The blood–brain barrier and blood–nerve barrier**

The blood–brain barrier is a barrier inhibiting the entry of intravenously administered dyes into the CNS parenchyma. Using horseradish peroxidase as a tracer, Reese & Karnovsky (1967) demonstrated that the barrier is located at the level of the CNS vascular endothelium. They concluded that the impermeability of the endothelium resulted from the presence of tight interendothelial junctions and a lack of micropinocytosis in the endothelial cells. Other elements, including the endothelial basement membrane and the perivascular glia limitans, contribute to the layered structure at the blood–brain interface, but do not appear to contribute significantly to the functional blood–brain barrier. In the PNS an analogous blood–nerve
barrier is present in the peripheral nerve, but not in the spinal roots or dorsal root ganglia (Waksman, 1961; Olsson, 1968; Jacobs, MacFarlane & Cavanagh, 1976). These barriers limit the access of circulating antibodies to the nervous system, but do not appear to limit T cell access, as activated T cells of any specificity can enter the normal CNS parenchyma (see below).

**Immunological surveillance of the nervous system by T cells**

Studies on the migration of labelled T cells following intravenous injection have shown that activated T cells of any specificity enter the normal CNS parenchyma as early as 3 h after injection (Wekerle et al., 1986; Hickey, Hsu & Kimura, 1991; Ludowyk, Willenborg & Parish, 1992). Thus, T cell traffic in the CNS appears to be governed by the same principle as applies to other organs, namely that activated T cells preferentially migrate from the blood into tissues, whereas resting cells exit in lymph node high-endothelial venules (Mackay, Marston & Dudler, 1990). Low numbers of T cells are consistently demonstrable in normal human and rat brains (Booss et al., 1983; Lessmann et al., 1986), indicating that the CNS is continuously patrolled by activated T cells (Wekerle et al., 1986). This conclusion is also supported by studies in radiation bone marrow chimeras (Lassmann et al., 1993).

**MHC expression and antigen presentation in the nervous system**

Having entered the nervous system, T cells will cause disease only if they recognize their specific antigens in the context of MHC molecules. CD8+ T cells recognize antigen in the context of class I MHC molecules, and CD4+ T cells recognize antigen in the context of class II MHC (Ia) molecules. Compared to other organs, the CNS exhibits a low level of MHC antigen expression (Pizarro et al., 1961; Wong et al., 1984).

**Neurones**

Neurones do not express MHC class I or class II antigens either in situ or after exposure to interferon-γ (IFN-γ) in vitro (Wong et al., 1984; Bartlett, Kerr & Bailey, 1989). The absence of such MHC antigen expression indicates that neurones cannot be targets of a conventional MHC-restricted specific T cell attack. However, neurones can be destroyed by natural killer cells through an unknown targeting mechanism (Hickey et al., 1992a).
Astrocytes

Astrocytes do not normally express MHC antigens in situ but can be induced to express both class I and class II antigens after exposure to IFN-γ in vitro (Wong et al., 1984). After being induced to express class II antigen, rat astrocytes are capable of presenting myelin basic protein (MBP) to MBP-specific CD4+ T cells and inducing the proliferation of these T cells in vitro (Fontana, Fierz & Wekerle, 1984; Fierz et al., 1985). However, Sedgwick et al. (1991a) have shown that the in vitro antigen-presenting capacity of rat astrocytes does not apply for naive CD4+ T cells. Although human astrocytes expressing class II antigen can present MBP to MBP-specific T cells, they do not induce T cell proliferation but inhibit it (Weber et al., 1994). Despite these in vitro findings, it is doubtful whether astrocytes have an antigen-presenting role in vivo, because they do not express detectable MHC class II antigen in inflammatory lesions (Matsumoto, Ohmori & Fujiwara, 1992).

Oligodendrocytes

Oligodendrocytes do not express MHC antigens in situ (Wong et al., 1984). Under standard in vitro conditions, oligodendrocytes can be induced by IFN-γ to express class I but not class II antigen (Wong et al., 1984; Turnley, Miller & Bartlett, 1991); however, in the presence of glucocorticoid, IFN-γ induces the expression of class II MHC molecules (Bergsteinsdottir et al., 1992).

Schwann cells

Exposure of Schwann cells to IFN-γ in vitro increases the expression of class I MHC antigen and induces the expression of class II antigen (Armati, Pollard & Gatenby, 1990). Furthermore, Schwann cells expressing class II antigen can present the P2 myelin protein to P2-specific CD4+ T cell lines (Argall et al., 1992).

Endothelial cells

In the normal CNS, vascular endothelial cells express MHC class I antigen but not class II antigen (Lassmann et al., 1991; Graeber et al., 1992), except in the guinea pig, where occasional endothelial cells express class II antigen (Sobel et al., 1984). After being induced to express Ia antigen by IFN-γ, murine cerebral vascular endothelial cells can present MBP to MBP-sensitized T cells in vitro (McCarron et al., 1985, 1986).
Microglia

Microglia are bone-marrow-derived cells that are resident in the CNS parenchyma and that phenotypically resemble monocytes and tissue macrophages (Perry, Hume & Gordon, 1985). However, in the mature animal there is no major turnover or replacement of resident microglia by bone-marrow-derived cells, even after severe CNS inflammation (Matsumoto & Fujiwara, 1987; Lassmann et al., 1993). Microglia have a dendritic or ramified morphology and are present throughout the grey and white matter. Microglial cell processes are also a minor component of the perivascular glia limitans, which mainly consists of astrocytic foot processes (Lassmann et al., 1991).

In general, class II MHC antigen expression is undetectable on microglia in the normal rat CNS, whereas it is readily detectable on morphologically similar dendritic cells in the interstitial connective tissues of a wide range of other organs (Hart & Fabre, 1981; Lassmann et al., 1986). However, some degree of class II antigen expression can be detected on microglia in the normal Brown Norway rat (Sedgwick et al., 1993) and in the normal human CNS (Hayes, Woodroffe & Cuzner, 1987; Graeber et al., 1992). There is also some expression of MHC class I antigen on microglia in the normal human CNS (Graeber et al., 1992). In experimental animals, an upregulation of microglial class I and class II antigen expression occurs following various insults to the nervous system, including experimental autoimmune encephalomyelitis (EAE) (Matsumoto et al., 1986; Vass et al., 1986; McCombe et al., 1992; Gehrmann et al., 1993), peripheral nerve transection (Streit, Graeber & Kreutzberg, 1989a, b), ischaemia (Gehrmann et al., 1992) and experimental autoimmune neuritis (Gehrmann et al., 1993). After such insults microglia also become activated to proliferate (Graeber et al., 1988b; Sedgwick et al., 1991b; McCombe, de Jersey & Pender, 1994), upregulate the expression of complement receptor type 3 (CR3) (Graeber, Streit & Kreutzberg, 1988a) and express other macrophage markers, such as ED1 (Graeber et al., 1990; Lassmann et al., 1993). Uregulated microglial class II MHC antigen expression has also been found in a wide range of human disorders, including multiple sclerosis, Alzheimer’s disease and Parkinson’s disease (Hayes et al., 1987; McGeer, Itagaki & McGeer, 1988). Reid et al. (1993) have shown that microglia can be activated and induced to proliferate and/or undergo apoptosis (programmed cell death) by stimulation of CR3.

The similarities between microglia and macrophages have raised the possibility that microglia may act as antigen-presenting cells. After being induced to express class II MHC antigen by IFN-γ, microglia have been reported to be capable of presenting antigen to T cells in vitro (Frei et al., 1987; Matsumoto et al., 1987). Recent studies have shown that microglial cells are not necessarily in the CNS do not necessarily in the CNS. In the periphery, microglial cells may serve as antigen-presenting cells (Markmann et al., 1994), as occur in the testes, salivary glands or the gastrointestinal tract. Perivascular and intraparenchymal microglial cells are also present in regions where the gliovascular system is thought to have a role in the immune response (Kleinschmidt et al., 1992).

Perivascular and Intravascular Microglia

Recent studies have shown that microglial cells in the CNS are not necessarily in the CNS. In the periphery, microglial cells may serve as antigen-presenting cells (Markmann et al., 1994), as occur in the testes, salivary glands or the gastrointestinal tract. Perivascular and intraparenchymal microglial cells are also present in regions where the gliovascular system is thought to have a role in the immune response (Kleinschmidt et al., 1992).

Studies on F1 hybrid mice have shown that bone marrow-derived cells are essential for the induction of EAE (Myers et al., 1988; Myers, Dobyns & Silver, 1988). The bone-marrow-derived cells are likely to be perivascular and intraparenchymal microglial cells, which are believed to be involved in the migration of cells in the CNS (Kleinschmidt et al., 1992; Kimura, 1988). It has been shown that bone-marrow-derived macrophages and microglial cells in the CNS of recipients of MBP-specific T cell lines are induced, albeit less efficiently, than in the recipients of MBP-specific T cell lines (Kimura, 1988). Therefore, bone-marrow-derived cells may be the antigen-presenting cells in the CNS.
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1987; Matsumoto et al., 1992), although in the experiments of Matsumoto et al. (1992) T cell proliferation was inhibited when higher numbers of microglial cells were used. The presence of class II antigen expression does not necessarily indicate an ability to upregulate the immune response, as there is evidence that such expression on non-specialized antigen-presenting cells may serve as an extrathymic mechanism for maintaining self tolerance (Markmann et al., 1988). Whether parenchymal microglia have an upregulatory or downregulatory effect on the immune response in vivo is unknown at present.

Perivascular and meningeal macrophages

Recent studies have indicated that perivascular macrophages and meningeal macrophages are the major antigen-presenting cells in the CNS. The term ‘perivascular macrophages’ refers to cells that constitutively express class I and class II MHC antigens and standard macrophage markers and that are located in the Virchow–Robin perivascular space between the vascular basement membrane and the parenchymal basement membrane of the glia limitans (Graeber, Streit & Kreutzberg, 1989; Graeber et al., 1992; Hickey, Vass & Lassmann, 1992b). These are the same cells that Hickey & Kimura (1988) called ‘perivascular microglia’. They are distinguishable from parenchymal microglia by their location, morphology and constitutive expression of standard macrophage markers. Similar macrophages are also present in the leptomeninges (Hickey & Kimura, 1988; Graeber et al., 1989).

Studies on F1-to-parent bone marrow chimeras as recipients of MBP-specific T cells have shown that histocompatibility between the recipient’s bone-marrow-derived cells and the donor T cells is sufficient for the induction of EAE (Hinrichs, Wegmann & Dietsch, 1987; Hickey & Kimura, 1988; Myers, Dougherty & Ron, 1993). In these chimeras the histocompatible bone-marrow-derived cells in the CNS are virtually confined to the perivascular and meningeal macrophage populations, as there is minimal settlement of these cells into the parenchymal microglial population (Hickey & Kimura, 1988). Therefore, these studies indicate that the perivascular macrophages and meningeal macrophages are major antigen-presenting cells in the CNS. Studies using parent-to-F1 bone marrow chimeras as recipients of MBP-specific T cells have indicated that EAE can also be induced, albeit less efficiently, when there is histocompatibility only between the recipient’s resident parenchymal cells and the donor T cells (Myers et al., 1993). These studies were interpreted as indicating that endothelial cells or astrocytes can act as antigen-presenting cells in vivo; however, it remains possible that radiation-resistant parenchymal microglia may be the antigen-presenting cells in this model.
Adhesion molecule expression and cytokine production in the nervous system

Adhesion molecule expression and cytokine production are important in the evolution of an immune response; however, the nervous system does not appear to differ from other organs in these respects (Fabry, Raine & Hart, 1994).

Access of circulating antibody to the intact nervous system

It is widely believed that the blood–brain barrier and blood–nerve barrier limit the access of circulating antibody to the normal nervous system. However, Reid et al. (1993) have recently reported that an anti-CR3 antibody readily gains access to the normal CNS through an unknown mechanism. Levine et al. (1991) found that circulating anti-viral antibody can enter the CNS and mediate the clearance of alphavirus infection from neurones in the absence of specific cell-mediated immunity but it was unknown whether the blood–brain barrier was intact.

Lymphatic drainage of the nervous system

Classically, the nervous system has been considered to lack lymphatic drainage; however, recent studies indicate that the magnitude of outflow of labelled protein from the CNS to the deep cervical lymph is much greater than was previously appreciated (Csern & Knopf, 1992). Gordon, Knopf & Csern (1992) have shown that, under conditions of normal blood–brain barrier permeability, ovalbumin evokes a greater serum antibody response when introduced into the brain or cerebrospinal fluid than when introduced into extracerebral sites. Priceas (1979) observed that thin-walled channels resembling lymphatic capillaries and containing lymphocytes and macrophages were present within the perivascular spaces of the CNS of patients with various neurological disorders. He suggested that the perivascular spaces may serve the same function in the CNS as lymphatic vessels serve in other tissues and that lymphocytes may normally circulate through these channels. However, it is unknown whether the channels ultimately drain into the cervical lymph nodes.

Downregulation of the immune attack within the nervous system

Downregulation within the nervous system itself may play an important role in limiting the immune attack (Wekerle, 1988). Apoptosis of T cells occurs

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in the CNS in response to inflammation due to, for example, Scrivani et al. (1994). This process selectively depletes T cells from the CNS, allowing clinical recovery to occur (Farrell & Newman, 1991). Selective elimination of T cell death receptors expressing cells to the nervous system (Tabi et al., 1994) and proliferation with interferon-2 results in a state of T cells that a state of T cells expressing class II molecules can still express but which could also be expanded. It is hypothesized that this is a self-limited, T-cell mediated mechanism general mechanism (Cook, 1992; Pender, 1992) and may contribute to recovery (Nguyen, McCann, 1991).

Conclusions

Although the brain is a local site that is exempt from the immune response, as are those in other organs and subcellular compartments, it is a potential target for autoimmune neurological disease. It is patrolled by activated immune antibodies. Perivascular spaces can be readily inducible by insults, it is unknown whether the immune response occurs; selectively eliminating T cells recovery from EAE. Other target organs may occur in other self-limited diseases.
in the CNS in acute EAE and may contribute to the subsidence of inflammation during spontaneous recovery (Pender et al., 1991, 1992; Schmied et al., 1993). Furthermore, there is evidence that the apoptotic process selectively eliminates autoreactive T cells from the CNS during clinical recovery (Tabi, McCombe & Pender, 1994). The mechanism for this selective elimination is unknown, but one possibility is activation-induced T cell death resulting from interaction with non-specialized antigen-presenting cells that fail to deliver the co-stimulatory signal (Pender, 1993; Tabi et al., 1994). Ohmori et al. (1992) found that there is little T cell proliferation within the CNS in acute EAE. As cells expressing the interleukin-2 receptor outnumbered proliferating T cells, they concluded that a state of T cell anergy is induced by interaction with glial cells expressing class II MHC antigen. However, as T cells undergoing apoptosis can still express cell surface molecules (Pender et al., 1992), their results could also be explained by activation-induced T cell apoptosis. It has been hypothesized that T cell apoptosis in the target organ may also occur in other self-limited, T-cell-mediated autoimmune diseases and that it may be a general mechanism for maintaining extrathmic tolerance (Pender et al., 1992; Pender, 1993). Macrophage apoptosis also occurs in the CNS in EAE and may contribute to the downregulation of this autoimmune disease (Nguyen, McCombe & Pender, 1994).

Conclusions

Although the brain is classically regarded as an immunologically privileged site that is exempt from immune surveillance, recent studies indicate that immune responses in the nervous system proceed in a similar manner to those in other organs. As a consequence of the diversity of specialized cells and subcellular components in the nervous system, there is a wide range of potential target antigens and clinical syndromes in autoimmune neurological disease. Despite the blood–brain barrier, the CNS is continuously patrolled by activated T cells and may be accessed by certain circulating antibodies. Perivascular macrophages and meningeal macrophages appear to be the main antigen-presenting cells. Although parenchymal microglia can be readily induced to express class II MHC antigen in vivo after a variety of insults, it is unknown whether they upregulate or indeed downregulate the immune response in the CNS. Finally, autoreactive T cells may be selectively eliminated from the CNS by apoptosis during spontaneous recovery from EAE. It has been hypothesized that T cell apoptosis in the target organ may be a general protective mechanism that also operates in other self-limited T-cell-mediated autoimmune diseases.
References


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