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MICROGLIA : IMMUNOREGULATORY CELLS IN THE CENTRAL NERVOUS SYSTEM

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INTRODUCTION

Microglia are one of three types of glial cells in the central nervous system (CNS). Although the origin of the cells is still controversial, several lines of evidences suggest that they are bone marrow-derived, monocyte-macrophage lineage cells that enter the brain during embryonic development and differentiate into ramified resting microglia through a series of morphologic transformations. After the development of isolation and culture techniques for microglia, many reports have indicated their morphological and functional similarities to monocyte-macrophages. They have complement receptors recognized with Mac 1 or OX42 monoclonal antibody, Fc receptors (Suzumura *et al.*, 1987), CD4 (Sawada *et al.*, 1992b) and CD14 antigens on their surface (unpublished observation), and react with the antibodies against surface molecules of macrophages such as F4/80, ED1, ED2, and EMB11(Austin *et al.*, 1981, Perry *et al.*, 1985, Dijkstra *et al.*, 1985, Imamura *et al.*, 1990). Microglia are also identified by binding with lectins, such as RCA-1 lectin and GSA-1 lectin (Mannoji *et al.*, 1986, Streit *et al.*, 1987). They express class I major histocompatibility complex (MHC) antigens and are induced to express class II MHC antigens (Suzumura *et al.*, 1987). Microglia phagocytose letex beads *in vitro* and are considered to remove remnants as phogocytic cells during the neurogenesis. Furthermore, they are regulated in growth, differentiation and activation by the same cytokines as are monocyte-macrophages (Sawada *et al.*, 1990, 1999, Suzumura *et al.*, 1990, 1991, 1998), and produce the same monokines, such as interleukin-1 (IL-1), IL-6 and tumor necrosis factor (TNF)α as macrophages do (Giulian *et al.*, 1986, Heiter *et al.*, 1988, Frei *et al.*, 1989, Sawada *et al.*, 1989, 1992a, Tomozawa *et al.*, 1995). They also produce IL-12 (Suzumura *et al.* 1998) and IL-18 (Suzumura *et al.* 2001), the cytokines which regulate differentiation of T helper cells, and several chemokines. Therefore, microglia are considered to play similar roles as macrophages in the CNS, functioning as scavenger cells, inflammatory cells, antigen-presenting cells, and immunoregulatory cells. In addition, microglia may function as effector cells that induce demyelination or neuronal degeneration, and may also play a major part in the development of gliosis via secreting cytokines or some other soluble factors (Giulian *et al.*, 1985, Selmaj *et al.*, 1990, Suzumura *et al.*, 1993a). In this review, we focused on the immunoregulatory functions, including antigen presentation and cytokine production, of microglia in physiological and pathological conditions in the CNS.

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DEVELOPMENT AND DIFFERENTIATION OF MICROGLIA

In rodents, microglia first appear near the choroid plexus and subarachnoid space and periventricular area in the late embryonic stage. They then migrate into the brain parenchyma and increase in number, reaching a maximum on postnatal day 10–14. Thereafter, they gradually decrease in number by postnatal day 28 and become ramified cells (Ling *et al.*, 1981, Perry *et al.*, 1985, Imamura *et al.*, 1990). Most antibodies against macrophages recognize ameboid microglia in the early developmental stage but do not react with ramified microglia in the late developmental stage, suggesting that the ameboid microglia lose some macrophage antigen to become resting microglia (Imamura *et al.*, 1990). In the case of injury or neuronal degeneration, ameboid microglia around degenerated neurons again acquire reactivity to these antibodies (Sedgwick *et al.*, 1991, Gehrmann *et al.* 1992). These ameboid microglia in the pathological lesions are mostly class II MHC antigen positive (Matsumoto *et al.*, 1986, Streit *et al.*, 1989a, b), while the ramified microglia are negative (Imamura *et al.*, 1990), and are considered to be in an activated form. Another type of microglia, the rod-shaped microglia, are observed in the brains of certain viral or spirochete infection (Schmidt *et al.*, 1976).

We have established the isolation and culture methods of purified microglia from neonatal mouse mixed glial cell cultures (Suzumura *et al.*, 1987), and showed that similar morphological transformation was reproduced *in vitro*. We have investigated the effects of various stimulants including cytokines on morphological changes, on proliferative activity and on functional changes of microglia. Cytokines which induced proliferation, such as macrophage colony-stimulating factor (M-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF), induced morphological changes to rod-shaped microglia (Suzumura *et al.*, 1990, 1991). Most of M- and GM-CSF-induced rod-shaped microglia incorporated bromodeoxyuridine in their nuclei, suggesting that they are proliferating (Suzumura *et al.*, 1990). The agents which stimulate activation of microglia, such as lipopolysaccharide, phorbol ester and interferonγ (IFNγ), induced morphological changes to ameboid form, though they did not induce proliferation. The unknown factors in astrocyte culture supernatant induced morphological changes to ramified shape, but did not induce either proliferation or activation of microglia. These observation suggest that the cytokines or other factors regulate morphological, as well as functional, changes to all three forms of microglia; activated ameboid, proliferating rod-shaped, and ramified resting microglia. Another unique morphological change is transformation into multinucleated giant cell. We have shown that stimulation of microglia with IL-4 or IL-13 along with colony-stimulating factors induce multinucleated giant cell (Suzumura *et al.*, 1999b).

Various cytokines are now known to induce proliferation of microglia *in vitro*. GM-CSF and M-CSF are most potent mitogens. IL-4 also induces proliferation of microglia while it suppresses other functions of microglia (Suzumura *et al.*, 1994). IL-2, when microglia are stimulated to induce IL-2 receptors by LPS, is capable to function as mitogen (Sawada *et al.*, 1995a). In order to examine which cytokines are responsible for the burst like proliferation of microglia during gliogenesis, we examined the expression of cytokine mRNA in normal developing mouse brain (Mizuno *et al.*, 1994a). The results indicated that M-CSF may play a major part in proliferation of microglia in normal developing brain. M-CSF may also function as a major mitogen in the increase of microglia after neuronal degeneration in the model of facial axotomy, because the microglial proliferation around degenerated neurons was not observed in M-CSF-deficient op/op mice (Raivich *et al.*,1994). It is still unclear whether or not other cytokines may function as mitogen for microglia in either physiological or pathological conditions *in vivo*.

EXPRESSION OF CLASS II MAJOR HISTOCOMPATIBILITY COMPLEX (MHC) ANTIGEN

In normal or unstimulated conditions *in vivo* and *in vitro*, microglia do not usually express class II MHC antigens on their surface while they express class I MHC antigens weakly. However, they are induced to express class II MHC antigens by IFNγ *in vitro* (Suzumura *et al.*, 1987). The induction of the expression was associated with the induction of mRNA for class II MHC antigens. IFNγ also enhances the expression of class I MHC antigens on microglia. Induction of class II MHC antigens were also observed *in vivo* in certain pathological conditions. In the brains of experimental allergic encephalomyelitis (EAE), microglia near the infiltrating T cells were reported to be class II MHC antigen positive (Matsumoto *et al.*, 1986, Butter *et al.*, 1991, Gehrmann *et al.*, 1993), suggesting T cell-derived cytokine, most probably IFNγ, could induce class II MHC antigen expression *in vivo* as well. There are increased number of microglia in or around facial nuclei after facial nerve axotomy. These cells were also reportedly class II MHC antigen positive (Streit *et al.*, 1989a, b). Since the blood-brain-barrier is not destroyed in this experimental condition and since there is no definite evidence that neural cells produce INFγ in the CNS, it is unlikely that IFNγ is responsible for the induction of class II MHC antigen expression in this model. Another candidate for the induction of class II MHC antigens in microglia is IL-3. We have shown that IL-3 dose-dependently induces surface expression and mRNA expression of class II MHC antigens in microglia, which is completely inhibited by anti-IL-3 antibody (Imamura *et al.*, 1994). Although we did not detect IL-3 or IL-3 mRNA in either microglia or astrocytes in the mouse system, it has been reported that rat microglia produce IL-3 *in vitro* (Gebicke-Haeter *et al.*, 1994), and that IL-3 mRNA is detected in some population of astrocytes and neurons by in situ hybridizaiton (Farrer *et al.*, 1989). Therefore, it is possible that IL-3 derived from degenerating neurons, reactive astrocytes or microglia themselves may induce class II MHC antigens on microglia in certain pathological conditions.

In contrast to IL-3, GM-CSF down-regulates IFNγ-induced class II MHC antigen expression in microglia. The suppression occurs in a dose-dependent manner, and is neutralized by anti-GM-CSF antibody (Imamura *et al.*, 1994). As we have shown previously, GM-CSF is produced by astrocytes (Ohno, *et al.*, 1990) and induces proliferation of microglia *in vitro* (Suzumura, *et al.*, 1990, 1991). It is possible that astrocytes down-regulate immunoregulatory functions of microglia. However, so far, there is no evidence that GM-CSF participates proliferation of microglia and suppression of their Ia expression in either physiological or pathological conditions *in vivo*.

Table 1. Effects of inhibitory cytokines on microglial functions.

	IL-4	IL-10	TGFβ
proiferation	↑	→	↓
enzyme activity	↑	↓	↓
IFNγ-induced Ia expression	↓	↓	↓
LPS-induced cytokine production	→	↓	↓
GM-CSF-induced IL-6 production	↓	↓	↓
cytokine receptor expression	→ (↑)*	↓	→

↑: up-regulate, →: no effect, ↓: down-regulate

* IL-4 upregulate IL-4 receptor, but do not affect the expression of other receptors, on microglia

All the macrophage deactivating cytokines, or inhibitory cytokines, such as IL-10, IL-4 and transforming growth factor β (TGFβ) down-regulated the INFγ-induced class II MHC antigen expression in microglia (Table 1) (Suzumura *et al.*, 1993b, 1994, Mizuno *et al.*, 1994b). As we and other groups have shown, astrocytes and microglia produce IL-10 (Mizuno *et al.*, 1994b) and TGFβ (Wahl *et al.*, 1991, Constam *et al.*, 1992), but neither cells produce IL-4 while both cell types express IL-4 receptors (Sawada *et al.*, 1993, Suzumura *et al.*, 1994). Thus, microglia may down-regulate their own immunoregulatory functions by themselves in autocrine fashion, or the astrocyte may suppress the functions of microglia in paracrine manner. It is also possible that invading T helper cells, especially T helper 2 (Th2), may down-regulate class II MHC antigen expression in microglia by these inhibitory cytokines.

ARE MICROGLIA ANTIGEN-PRESENTING CELLS IN THE CNS?

The immune response is initiated when protein antigen is presented to T cells by antigen presenting cells (APC) that takes place in lymphoid organs. The APC processes antigen, either foreign or self, by internalizing and digesting it into peptide fragments. Then processed peptide fragments are expressed on the surface of APC as a form of MHC-peptide complex. When the MHC-peptide complex interacts with T cell receptors (TCR), subsequent T cell activation occurs. Class II MHC molecules present antigen to CD4-positive T cells, while class I MHC molecules present antigen to CD8-positive T cells. Binding of the MHC-peptide complex to the TCR is critical, but not sufficient, for activation of T cells. There should be several co-stimulatory molecules that interact with the ligands on T cells for sufficient activation. These co-stimulatory molecules on APC are B7.1, B7.2, leukocyte function associated molecule 3 (LFA-3), intercellular adhesion molecule-1 (ICAM-1), ICAM-2 and ICAM-3. They bind to ligands on T cells to form ligand pairs such as B7.1-CD28, B7.2-CTLA4, LFA-3-CD2, ICAM-1, 2 or 3-LFA-1. Interaction of T cells and APC occurs in a MHC-restricted manner. The T cells recognize a foreign antigen only when the antigen is complexed with a self MHC molecules on APC. Therefore, the cells expressing class II MHC and co-stimulatory molecules constitutively are considered to be professional APC. Those include macrophage, B cells, dendritic cells, and Langerhans cells. Non-professional APC differ from the professional APC by expressing little or no MHC class II molecules constitutively, and by not having a complete set of co-stimulatory molecules. The candidates for the non-professional APC in the CNS are microglia, astrocytes and endothelial cells (Fontana *et al.*, 1984, Hickey *et al.*, 1985, 1988, Fierz *et al.*, 1985, Frei *et al.*, 1987, Matsumoto *et al.*, 1992). They do not usually express class II MHC antigen constitutively, although some population of microglia reportedly express class II MHC constitutively (Ford *et al.*, 1995). These cells have been shown to be induced to express class II MHC molecules with certain inflammatory cytokines, especially IFNγ (Fontana *et al.*, 1984, Fierz *et al.*, 1985, Frei *et al.*, 1987, Suzumura *et al.*, 1987), and also express some of the co-stimulatory molecules (De Simone *et al.*, 1995, Satoh *et al.*, 1995, Aloisi *et al.*, 1996). There are several evidences that endothelial cells (Sedgwick *et al.*, 1990), astrocytes (Fontana *et al.*, 1984), and pericytes (Fabry *et al.*, 1990) can process and present protein antigens to primed CD4-positive T cells *in vitro*, but the specific role of these cells as APC *in vivo* is still unclear. At least, astrocytes do not usually express class II MHC antigens *in vivo*, even in the presence of inflammatory cells (Hickey *et al.*, 1985). Since microglia have very similar characteristics to macrophage and are induced to express class II MHC antigens as discussed above, microglia are the most possible candidates for APC in the CNS. The expression of co-stimulatory molecules, such as B7, ICAM, LFA3 in microglia, but only some in astrocytes, further supports this

hypothesis. Aloisi et al (1996) detected B7-2, but not B7-1, in murine microglia only after stimulation with LPS and IFNγ. Satoh *et al.* (1995) have shown that human microglia, but not astrocytes, express both B7-1 and B7-2, suggesting that microglia is a much more suitable candidate for local APC in the CNS. In fact, microglia when stimulated with IFNγ reportedly presented antigen to ovalbumin-specific or MBP-specific T cells *in vitro* (Frei, *et al.*, 1987, Matsumoto *et al.*, 1992, Walker, *et al.*, 1995). Hickey and Kimura (1988) have shown elegantly that microglia functions as APC in pathological conditions *in vivo*. They used bone marrow chimera of EAE-susceptible and resistant animals, and found that EAE lesions developed only when the perivascular microglia were replaced with EAE-susceptible strain, suggesting that antigen presentation by perivascular microglia is critical for the development of EAE lesions.

PROFESSIONAL APC SUCH AS DENDRITIC CELLS OR MACROPHAGES PRODUCE IL-12 AND IL-18

IL-12 and IL-18 have been shown to be key cytokines in the development of autoimmune processes, regulating differentiation of naïve T cells into T helper 1 (Th1). To exert its activity, IL-12 needs to form heterodimer of P35 and P40; homodimer of P40 suppresses the functional heterodimer. Immature IL-18 is cleaved by caspase-1 to become functional mature IL-18 that induces differentiation of Th1 and cytotoxic activity of NK and T cells. We have shown that murine microglia produce both IL-12 and IL-18 upon stimulation with LPS (Suzumura *et al.*, 1998, 2001). LPS-stimulated microglia had bioactivity of IL-18 to induce INFγ production by thymocytes and splenocytes in synergism with IL-12. This suggested that microglia express caspase-1 as well. Interestingly, there was a group of microglia that produced only IL-12 P40, but not IL-12 P35. The population did not produce IL-18 even after LPS stimulation. Since we have shown neural cells do not produce IL-4 which induces Th2 responses, Th1 responses are likely to occur in the CNS. Microglia have at least 2 populations to regulate the differentiation of helper T cells.

CYTOKINE PRODUCTION AND EXPRESSION OF RECEPTORS FOR CYTOKINES BY MICROGLIA

Another reason that microglia are considered to be a immunoregulatory cell in the CNS is that they produce a variety of immunoregulatory cytokines (Table 2). Microglia produce IL-1, IL-5, IL-6, IL-10, TGFβ, and TNFα (Giulian *et al.*, 1986, Heiter *et al.*, 1988, Frei *et al.*, 1989, Sawada *et al.*, 1989, 1992a, 1993b, Mizuno *et al.*, 1994b, Wahl *et al.*, 1991, Tomozawa *et al.* 1995). Rat microglia reportedly produced IL-3 in culture. Only a trace amount of IL-1, but not the other cytokines, are detectable in the supernatant of unstimulated microglial culture. However, lipopolysaccharides, TNFα or IFNγ in some cases, induces cytokine production. Since microglia express receptors for most of these cytokines (Table 2), these may function as a autocrine regulator. They also express receptors for cytokines which are produced by astrocytes but not by themselves, such as GM-CSF and M-CSF. These cytokines, thus, may function as paracrine mediators (for the functions of these cytokines on microglia, refer to our previous review, Sawada *et al.* 1995b). Microglia also express receptor for IL-4, the cytokine produced by T cells, but not produced in the CNS. Thus, IL-4 may be a paracrine mediator exerting its effects only in the cases of inflammatory process in the CNS, but not in the normal brain. We have shown the production of IL-5 by microglia, which was upregulated by IFNγ. However, since we did not detect IL-5 receptors on neural cells, the functions of IL-5 in the CNS remained to be elucidated.

Table 2. Cytokine production and receptor expression in microglia.

	production	receptor expression	functions
IL-1	yes	yes	ND
IL-2	ND	yes**	growth
IL-3	no (yes)*	yes	activation
IL-4	no	yes	growth, suppression
IL-5	yes	no	ND
IL-6	yes	yes	ND
IL-7	ND	yes	ND
IL-10	yes	yes	suppression
TNFα	yes	ND (yes)	activation
IFNγ	no	ND (yes)	activaiton, morphology
TGFβ	yes	ND (yes)	suppression
M-CSF	yes	yes	growth, activation
GM-CSF	no	ND (yes)	growth, suppression

ND: not determined, ( ): most probably yes, *: reportedly yes, although we could not confirmed in our mouse system, **: inducible

THE ROLES OF MICROGLIA IN THE CNS CYTOKINE NETWORK

Both microglia and astrocytes produce the same cytokines, such as IL-1, IL-6, TNFα and TGFβ. However there are several differences in the response to stimulation in these two cell types. For example, microglia produce TNFα in response to lower doses of LPS and more rapidly than astrocytes. TNFα induces IL-6 production in astrocytes, but not in microglia (Sawada *et al.*, 1992a). Similarly, GM-CSF produced by astrocytes induces IL-6 production in microglia but not in astrocytes (Suzumura *et al.*, in perss). This indicates that microglia and astrocytes may mutually regulate their cytokine production. Since microglia appear in the earlier phase than in astrocytes under various pathological conditions, microglia may initiate the cascade of the cytokine actions in the cytokine network in the CNS. Inhibitory signals are also included in the network (Table 1). TGFβ produced by astrocytes and microglia, suppresses all the functions of microglia. It suppresses M- and GM-CSF-induced proliferation of microglia, LPS-induced activation of enzymatic activity in microglia, IFNγ-induced class II MHC antigen expression and cytokine production by microglia. TGFβ along with IL-4 and IL-10 is known to be a macrophage deactivating factor. Therefore, these cytokines may function as negative regulators in the CNS cytokine network by suppressing cytokine production and activation of microglia. In fact, it has been found that these inhibitory cytokines function on microglia differently. TGFβ seemed to be a total inhibitory factor (Suzumura *et al.*, 1993b). IL-10 suppressed cytokine production and IFNγ-induced class II MHC antigen expression in microglia, but did not suppress proliferation or activation of lysosomal enzyme in microglia (Mizuno *et al.*, 1994a). IL-4 also suppressed IFNγ-induced class II MHC antigen expression in microglia (Suzumura *et al.*, 1994). Unlike other inhibitory cytokines, IL-4 induced proliferation of microglia in either unstimulated or M-, or GM-CSF-stimulated conditions. IL-4 did not suppress LPS-induced cytokine produc-

tion, but it suppressed GM-CSF-induced IL-6 production by microglia (Suzumura *et al.*, 1996). We also found that IL-10, but not TGFβ or IL-4, suppressed the expression of cytokine receptors, as well (Sawada *et al.*, 1999). Thus, it would appear that all these three inhibitory cytokines regulate the functions of microglia in a distinct manner, and that IL-10 may be the most potent inhibitor for the functions of cytokines on microglia.

DOSE SUPPRESSION OF MICROGLIAL FUNCTION RESULT IN SUPPRESSION OF IMMUNE-MEDIATED INJURY OF THE CNS

As shown above, TGFβ and IL-10 suppressed the IFNγ-induced class II MHC antigen expression and LPS-induced cytokine production of microglia. Therefore, if microglia play a critical role in the development of immune-mediated injury as immunoregulatory cells or effector cells, suppression of microglial functions by TGFβ or IL-10 should result in the suppression of the disease process. As expected, these inhibitory cytokine successfully suppressed the development of EAE (Johns *et al.*, 1991, Martin *et al.*, 1995). It is not clear at this moment whether suppression of the induction of class II MHC is critical or suppression of cytokine production is essential for the inhibition of EAE. However, because cAMP elevating drugs such as pentoxifylline which suppress cytokine production by microglia but dose not suppress induction of class II MHC on microglia also suppress the development of EAE (Nataf *et al.*, 1993, Rott *et al.*, 1993), the suppression of EAE is more likey to occur via down-regulation of cytokine production by microglia. This indicates the significant roles of microglia as effector cells. Selmaj *et al.* (1988, 1991a, b) have shown that TNFα kills oligodendrocytes in culture, and that treatment with anti-TNFα antibody successfully suppress the development of EAE, suggesting that suppression of microglia-derived cytokines is critical for suppression of immune-mediated injury in the CNS. We have found that all the type of cAMP-elevating agents, either phosphodiesterase inhibitor or adenylate cyclase activator suppressed TNFα and nitric acid (NO) production by microglia (Suzumura *et al.*, 1999, Yoshikawa *et al.*, 1999) (Fig. 1). These drugs have also effectively suppressed the development of EAE and clinical relapse of multiple sclero-

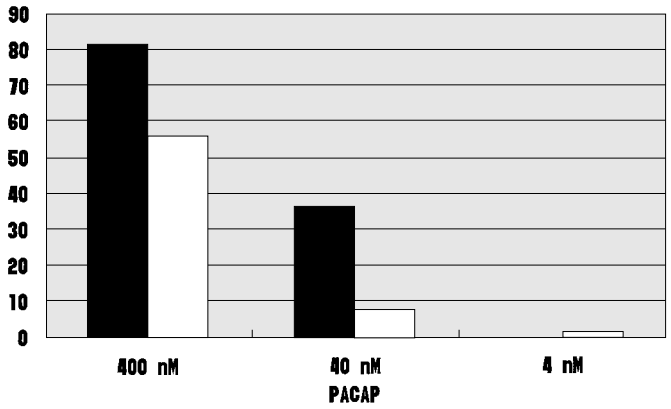

Fig. 1. Suppression of TNFα and NO production by microglia.
Microglia were stimulated with 1μg/ml LPS for 24h in the presence of the graded concentration of pituitary adenylate cyclase activating polypeptide (PACAP). The concentration of TNFα and NO were then measured. The bars indicate % suppression of TNFα (black) and NO (white).

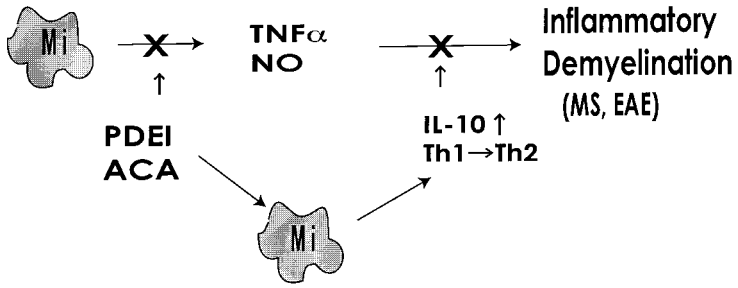

Fig. 2. Suppression of inflammatory demylination.
Phosphodiesterase inhibitors (PDEI) and adenylate cyclase activator (ACA) suppress TNFα and NO production by microglia. They also induce Th1 to Th2 shift and suppress relapses in the patients with multiple sclerosis, by suppressing production of IL-12 and enhancing IL-10 production.

sis (MS) (Suzumura *et al.*, 2000). We have analyzed the cytokine profile in CD4-positive T cells during the treatment of MS. The study showed that phosphodiesterase inhibitors induced Th1 to Th2 shift in CD4-positive T cells (Kikui *et al.* submitted for publication). Since we also found that phosphodiesterase inhibitors upregulate IL-10 and down-regulate IL-12 production by microglia (unpublished observation), this mechanism may involved in Th1 to Th2 shift and also in suppression in MS relapse (Fig. 2).

Microglia is also considered to be a target of HIV infection, because they exclusively express CD4 in the CNS. Evidence so far indicates that microglia, but not other neural cells are a major cell type that are infected with HIV either *in vitro* or *in vivo*. Thus, although the precise mechanisms of HIV-related neurological disorders are still unknown, it is possible that infection of microglia induces subsequent neuronal degeneration via secretion of cytokines, nitoric oxide or other neurotoxins (Wilt *et al.*, 1995). We have found that infection of murine astrocytes and microglia with the murine AIDS virus, LP-BM5 murine leukemia virus, induces cytokine production in the infected astrocytes and microglia (Suzumura *et al.*, 1998b). Furthermore, suppression of these cytokine production, especially TNFα production, by phosphodiesterase inhibitors or anti-TNFα antibodies resulted in the suppression of viral infection in glial cells (Fazely, *et al.*, 1991). Since TNFα enhances replication of HIV in the target cells via induction of nuclear factor, NF-κB which activate long terminal repeat (LTR) of HIV genome (Duh *et al.*, 1989, Peterson *et al.*, 1992), similar mechanisms may be involved in the infection of glial cells with the murine AIDS virus. This indicates that regulation of cytokine production of microglia can be a possible strategy for the treatment of some viral infection in the CNS. Phosphodiesterase inhibitor may be of use for this purpose (Han *et al.*, 1990, Dezube *et al.*, 1993).

We have found that the immunosuppressants, such as cyclesporine A or FK506 effectively suppressed CD4 antigen expression on microglia in a cell type specific manner (Sawada *et al.*, 1992b). Since the CD4 is considered as a receptor for HIV infection, down-regulation of this molecule by immunosuppressant may possibly suppress HIV infection in microglia. These agents, if modified to pass through the blood brain barrier, may prevent viral spread in the CNS and the development of AIDS-dementia complex.

CONCLUSIONS

Microglia is a possible candidate for the APC in the CNS. They produce a variety of immunoregulatory cytokines which function as autocrine or paracrine mediators to regulate the CNS cytokine network, and also function as effector molecules in pathological conditions. The regulation of the immunoregulatory functions of microglia can be useful tools to establish new strategies for treatment of various neurological disorders.

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