65 Weng, G. Z. (1996) *J. Biol. Chem.* 271, 26445–26448
66 Dessauer, C. W., Scully, T. T. and Gilman, A. G. (1997) *J. Biol. Chem.* 272, 22272–22277
67 Lambright, D. G. *et al.* (1996) *Nature* 379, 311–319
68 Wu, Z. L. (1995) *Proc. Natl. Acad. Sci. U. S. A.* 92, 220–224
69 Sharma, S. K., Klee, W. A. and Nirenberg, M. (1975) *Proc. Natl. Acad. Sci. U. S. A.* 72, 3092–3096
70 Avidor-Reiss, T., Nevo, I., Levy, R., Pfeuffer, T. and Vogel, Z. (1996) *J. Biol. Chem.* 271, 21309–21315
71 Avidor-Reiss, T., Nevo, I., Saya, D., Bayewitch, M. and Vogel, Z. (1997) *J. Biol. Chem.* 272, 5040–5047
72 Spiegel, A. M. (1998) in *G Proteins, Receptors, and Disease*, Humana Press
73 Toya, Y., Schwencke, C. and Ishikawa, Y. (1998) *J. Mol. Cell.* Cardiol. 30, 97–108
74 Wayman, G. A., Wei, J., Wong, S. and Storm, D. R. (1996) *Mol. Cell Biol.* 16, 6075–6082
75 Wei, J., Wayman, G. and Storm, D. R. (1996) *J. Biol. Chem.* 271, 24231–24235
76 Krengel, U. *et al.* (1990) *Cell* 62, 539–548
77 Sayle, R. A. and Milner-White, E. J. (1995) *Trends Biochem. Sci.* 20, 374
78 Kraulis, P. J. (1991) *J. Appl. Crystallogr.* 24, 946–950
79 Merritt, E. A. and Bacon, D. J. (1998) *Methods Enzymol.* 277, 505–524

Chemokines and chemokine receptors in the CNS: a possible role in neuroinflammation and patterning

Françoise Mennicken, Rich Maki, Errol B. de Souza and Rémi Quirion

Chemokines constitute a growing family of structurally and functionally related small (8–10 kDa) proteins associated with inflammatory-cell recruitment in host defence. In addition to their well-established role in the immune system, recent data suggest their involvement in the maintenance of CNS homeostasis, in neuronal patterning during ontogeny and as potential mediators of neuroinflammation, playing an essential role in leukocyte infiltration into the brain. Chemokines and their G protein-coupled receptors are constitutively expressed at low-to-negligible levels in various cell types in the brain. Their expression is rapidly induced by various neuroinflammatory stimuli, implicating them in various neurological disorders such as trauma, stroke and Alzheimer's disease, in tumour induction and in neuroimmune diseases such as multiple sclerosis or acquired immunodeficiency syndrome (AIDS). Here, **F. Mennicken, R. Maki, E. B. De Souza and R. Quirion** briefly summarize recent exciting findings in the field.

Chemokines regulate leukocyte/lymphocyte traffic and play a major role in homeostasis, inflammation and development of the immune system[1]. As in the immune system, chemokines and chemokine receptors in the CNS are constitutively expressed at low levels in astrocytes, microglia and neurones, or both, in the developing and adult brain and are induced by inflammatory mediators. Furthermore, chemokines and their receptors are upregulated in various neuroinflammatory diseases such as multiple sclerosis and acquired immune deficiency syndrome (AIDS), in brain tumours as well as in neurological disorders such as stroke and head trauma[2].

An overview of chemokines and chemokine receptors

The chemokines constitute a growing family of more than 40 distinct members divided into four distinct families on the basis of their structural conservation of specific cysteine residues[1–3] (Table 1). In addition to their chemotactic effects in the immune system, chemokines modulate a number of biological responses, including enzyme secretion, cellular adhesion, cytotoxicity, tumour cell growth, degranulation and T-cell activation[2,4].

The chemokines mediate their effects via G protein-coupled receptors of the seven transmembrane domain, rhodopsin-type superfamily[3,5] and have two main sites of interaction with their receptors. The low-affinity site appears to be responsible for the establishment of chemokine gradients on the surface of endothelial cells and within the extracellular matrix and facilitates by its interaction with the receptor the correct presentation of the second site, the high-affinity site essential for triggering signal transduction and receptor function[6].

The chemokines also interact with two types of non-signalling molecules. First, the Duffy antigen receptor for chemokines (DARC) is expressed on erythrocytes and endothelial cells and binds the different chemokines in order to limit chemokine blood levels[7]. Second, chemokines, which are highly basic molecules, interact physically with acidic extracellular components of endothelial cells. During this association, the chemokines are still active and can serve to establish a local concentration gradient from the source of chemokine secretion[2].

Localization and roles of the chemokines and their receptors in the brain

Chemokines and their receptors in the brain

Although numerous chemokines have been isolated from various neuronal cell lines[4], only a few are detected

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Table 1. Chemokines and their receptors

Family	Chemokine	Receptor
CXC or α chemokines	IL-8/NAP-1	CXCR1, CXCR2
	GRO-α/MGSA (mKC)	CXCR2
	GRO-β (mMIP-2α)	CXCR2
	GRO-γ (mMIP-2β)	CXCR2
	γIP-10	CXCR3
	SDF-1	CXCR4
CC or β chemokines	MIP-1α	CCR1, CCR4, CCR5
	MIP-1β	CCR5, CCR8
	LARC/MIP-3α	CCR6
	MIP-3β	CCR7
	MCP-1 (mJE)	CCR2, CCR4
	MCP-2	CCR1, CCR2
	MCP-3	CCR1, CCR2, CCR3
	MCP-4	CCR2, CCR3
	RANTES	CCR1, CCR3, CCR4*, CCR5
	Eotaxin	CCR3
	I-309 (mTCA3)	CCR8
C or δ chemokines	Lymphotactin	?
C or γ chemokines	Neurotactin/fractalkine	CX_3CR1

γIP-10, interferon γ-inducible protein 10 kDa; GCP, granulocyte chemoattractant protein; GRO, growth-related oncogene; IL-8, interleukin 8; LARC, liver and activation-regulated chemokine; mJE, murine homologue of MCP-1; mKC, murine homologue of GRO-α; mTCA3, T-cell activation gene 3, mouse homologue of human I-309; MCP, monocyte chemoattractant protein; MGSA, melanocyte growth stimulatory activity; MIP, macrophage inflammatory protein; NAP-1, neutrophil-activating peptide 1; RANTES, regulated upon activation, normal T cells, expressed and secreted; SDF-1, stromal cell-derived factor 1. *Depending on the authors, CCR4 was defined as a receptor for RANTES or not.

under basal conditions in the CNS. Table 2 summarizes the data available concerning the localization of chemokines and their receptors in the brain. Chemokines are mostly expressed by astrocytes and microglial cells, or both, whereas their receptors are also expressed by neuronal cells (Table 2, Refs 8–21). Chemokines and their receptors are also localized in the brain on endothelial cells and fibroblasts of capillary vessels and on circulating leukocytes under certain circumstances[4,22].

Intracerebral injection of chemokines and transgenic mice: a major role in leukocyte recruitment

Chemokines, in conjunction with integrins and endothelial cell-adhesion molecules, are believed to control the circulation of leukocytes through tissues[2,23,24]. Intra-hippocampal injections of human recombinant chemokines in mouse confirmed their role in leukocyte recruitment in brain parenchyma: monocyte chemoattractant protein-1 (MCP-1), interferon-γ-inducible protein-10 (IP-10) and RANTES (regulated upon activation, normal T-cells, expressed and secreted) are chemoattractant for monocytes, and interleukin-8 (IL-8) and macrophage inflammatory protein-2 (MIP-2) provoke a dramatic polymorphonuclear leukocyte (PMN) recruitment associated with a breakdown of the blood–brain barrier (BBB) that could be attenuated by prior depletion of circulating leukocytes[25].

Similarly, transgenic mice overexpressing mKC [mouse homologue of human Growth Related Oncogene (GRO)-α] or MCP-1 (under control of the myelin basic protein promoter) show specific leukocyte recruitment (neutrophil for mKC and monocyte for MCP-1) without additional stimuli, one third dying before one year of age[22,26,27]. Interestingly, some mKC transgenic mice develop neurological symptoms characterized by progressive postural instability, clumsiness and rigidity without weakness; these symptoms result in impaired nutrition and give rise to a terminal wasting syndrome. Neuropathological examination revealed chronic neutrophil infiltration, astroglial and microglial activation, BBB disruption but no significant changes in neurones, myelin or axons[27].

Knockout mice: role of chemokines in inflammation and embryonic development

Mice deficient in a particular chemokine confirm their importance in regulating the movement of inflammatory cells into tissues[2]. Briefly, MIP-1α, MCP-1, eotaxin, CCR1, CCR2, CCR5 and CXCR2 knockout mice show deficiencies in leukocyte recruitment according to their chemoattractant specificity and abnormalities in cytokine expression in several inflammatory models[28–34].

Recently, knockout mice models highlighted the biological importance of chemokines beyond their role in inflammation. In contrast to the chemokine knockout mice described above, which developed normally, mice deficient in stromal cell-derived factor 1 (SDF-1) or CXCR4 (so far, the only known receptor for SDF-1) died perinatally[35,36]. From embryonic days E13–E14, $SDF\text{-}1^{-/-}$ mice manifest defects in B-cell lymphopoiesis and in the recruitment of haematopoietic progenitors from fetal liver into the bone marrow, as well as defects in gastrointestinal vascularization and ventricular septum, revealing a crucial role for SDF-1 in embryonic development[35,36]. $CXCR4^{-/-}$ mice demonstrate the same abnormalities, in addition to an abnormal cerebellar development[36,37]. Cerebella of $CXCR4^{-/-}$ mice present premature migration of the external granular cells into the internal granular layer at E17, an event that normally occurs after birth. Abnormal clustering of neurones is also observed despite the presence of intact radial glia[37]. Interestingly, CXCR4 mRNA is expressed in proliferative areas of the brain including the cerebellum, cerebral cortex, hippocampus and spinal cord during development[37,38]. These data highlight a role for chemokines in neuronal cell migration, axonal guidance and patterning during embryonic development.

In vitro *role of chemokines in homeostatic environment and in the differentiation and migration of brain cells*

Analogies between haematopoiesis and neuropoiesis during embryogenesis have been proposed on the basis of their mechanistic similarities and the effects of cytokines on the differentiation of neuronal subsets[39]. The initial development of both systems requires the

migration of multipotent progenitor cells and might be influenced by shared chemokine receptors prior to the formation of the BBB.

Cell culture studies support a role for chemokines in the differentiation and migration of brain cells. For example, IL-8 is able to enhance the survival of neurones and the number of microglial and astroglial cells in rat hippocampal cultures[40] and a direct effect of IL-8 on neuronal growth is likely as CXCR2 receptors are present on neurones in the hippocampus (as shown in human brain[11]). Recently, Bolin *et al.*[41] showed that RANTES elicited migration and differentiation of mouse embryonic dorsal root ganglia (DRG) cells *in vitro*. Moreover, RANTES is detected immunohistochemically in embryonic DRG and could stimulate intracellular Ca^{2+} mobilization, indicative of a direct receptor-mediated event[41]. Mouse astrocytes also migrate *in vitro* in response to physiological concentrations (nanomolar or less) of MCP-1, mKC, T-cell activation gene 3 (mTCA3) and MIP-1α (Refs 16, 42). In addition, murine astrocytes express the mRNA for CCR1, one of the receptors of MIP-1α, which suggests a possible direct effect of MIP-1α on astrocyte migration[16]. Microglial chemotaxis has also been demonstrated *in vitro* in response to neurotactin[18] and MCP-1 (Ref. 43).

Among chemokines and their receptors, neurotactin and its receptor CX_3CR1 are of particular interest as neurotactin is the only chemokine expressed in higher amounts in the CNS than in the immune system and periphery[19]. Moreover, neurotactin (mRNA and protein) is present in neurones whereas CX_3CR1 mRNA is expressed in microglia[18,20]. It is also known that neurotactin can stimulate microglial chemotaxis and elevate intracellular Ca^{2+} levels in CHO cells expressing CX_3CR1; these effects are blocked by anti-CX_3CR1 antibodies[18]. These data, along with the observation that a spinal cord injury induces an upregulation of the neurotactin protein and CX_3CR1 mRNA, suggest a putative role for neurotactin and CX_3CR1 in cell–cell interaction between neurones and microglia[18].

Chemokines in CNS diseases

Common features

Leukocyte infiltration into the CNS is a crucial step in response to diverse challenges, including infection, trauma and stroke, as well as immune-mediated disorders

Table 2. Chemokines and chemokine receptors in the brain

Family	Chemokine/receptor	Localization	Refs
CXC	IL-8 mRNA	Human fetal and adult microglial cultures	8
	CXCR2 protein	Human astrocyte, microglial and fetal brain cultures	9, 10
		Human neurones from hippocampus (pyramidal cells), dentate nucleus of the cerebellum, paraventricular nucleus, locus coeruleus, pontine nuclei, anterior horn, intermediolateral cell column, and dorsal nucleus of Clarke of the spinal cord	11
	CXCR2 mRNA	Human fetal brain cultures	10
	CXCR4 protein	Neurones and astrocytes in human fetal brain cultures	12
		Neurones, microglia and some reactive astrocytes in human hippocampus, cerebellum and basal ganglia; human microglial cultures but not human oligodendrocyte cultures	13
	CXCR4 mRNA	Human brain cultures and human microglial cultures	13, 14
CC	MCP-1 mRNA	Human fetal microglia cultures	15
	MIP-1α and MIP-1β mRNA	Human fetal microglia cultures	15
	CCR1 but not CCR4 mRNA	Mouse astrocyte cultures	16
	CCR3 protein	Microglia from human brain cultures and adult brain	14
	CCR3 mRNA	Microglia from human brain cultures	14
	CCR5 protein	Microglia from human brain cultures	14
		Astrocytes and neurones in human and macaque cerebellum and hippocampus as few microglial cells	17
	CCR5 mRNA	Microglia from human brain cultures	14
CX_3C	Neurotactin protein and mRNA	Neurones and astrocytes of adult mouse, rat and human brain (cortex, hippocampus, caudate putamen, thalamus, olfactory bulb)	18–20
	CX_3CR mRNA	Rat microglial cultures	18
DARC protein		Cerebellar purkinje cells	21

DARC, Duffy antigen receptor for chemokines; IL-8, interleukin 8; MCP, monocyte chemoattractant protein; MIP, macrophage inflammatory protein.

such as multiple sclerosis (MS). The ability of chemokines to control precisely the movement of inflammatory cells suggests that chemokines and their receptors might provide novel targets for CNS therapeutic intervention. Interestingly, the type of inflammatory infiltrate that characterizes a specific disease is controlled, in part, by the subgroup of chemokines expressed in a pathological tissue, in a spatially and temporally dependent manner[2,44]. Following CNS inflammation or injury, several modifications occur in microglia and astrocytes representing the transformation from resting to activated states[45]. Although an inflammatory response is necessary for the resolution of a pathogenic event, the toxic nature of many products secreted by various cells implicated in these events can cause significant damage to tissues[45]. In many infectious diseases, pathogenic organisms can express chemokine- and chemokine-receptor-like molecules that can interact with chemokines and their receptors[46,47].

Recent reviews have summarized the role of chemokines in inflammatory processes occurring in the CNS (Refs 22, 44, 45, 48). Accordingly, the focus here is on the most recent data on the possible role of chemokines in various CNS diseases.

Cerebral ischaemia/reperfusion injury

Following focal or global ischaemia, GRO-α and MCP-1 mRNAs are rapidly expressed[49,50]. MCP-1 mRNA is initially expressed in astrocytes surrounding the ischaemic tissue and subsequently in infiltrating macrophages and reactive microglia in the infarcted tissue[50,51].

Reperfusion following transient ischaemia is a frequently encountered clinical condition that often causes greater tissue damage than persistent ischaemia. Matsumoto *et al.*[52] showed that IL-8 level is locally produced in reperfused rabbit brain tissue and that a neutralizing anti-IL-8 antibody significantly reduced brain oedema and infarct size. Furthermore, systemic increases of blood mononuclear cells expressing IL-8 mRNA and of IL-8 levels in patients with recent ischaemic stroke suggested the involvement of IL-8 in the recruitment of blood polymorphonuclear cells to ischaemic loci[53].

Taken together, these studies suggest the deleterious nature of chemokines in the cerebral ischaemia/reperfusion tissue injury by increasing leukocyte infiltration and subsequent neuronal damage[54].

CNS trauma

Twenty-four hours following a mechanical trauma to the cerebral cortex, an astroglial reaction begins and activated mononuclear phagocytes (derived from blood-borne monocytes) and microglia infiltrate the sites of injury[55].

Stab wounds in rodent brain have provided a reliable model to study traumatic injuries to the CNS. GRO-α, IP-10, MCP-1, MIP-1α, MIP-1β and RANTES mRNAs have been shown to be upregulated as early as 3 h after a cerebral stab injury[55,56]. Astrocytes in proximity to the stab express MCP-1 and MIP-1α but not RANTES which is only expressed by macrophages at the site of injury[56]. Interestingly, stab injury in neonates failed to induce MCP-1 expression and astrogliosis. This suggests that chemokine gene expression may be one component of the astrocyte activation programme[57]. There is also a close relationship between leukocyte infiltration and elevated levels of MCP-1, MIP-1β and RANTES mRNAs following brain trauma[55]. Moreover, following spinal cord injury, the expression of chemokines (MCP-1, MCP-5 and IP-10 mRNAs) precedes the influx of circulating leukocytes into the injured site[58], confirming that chemokines may be important to trigger leukocyte activation.

A recent study by Harrison *et al.*[18] revealed that, following facial motor nerve axotomy, the levels of neurotactin (secreted and membrane-anchored forms) and of CX_3CR1 mRNA are increased in the facial nucleus in parallel to cellular and morphological changes in microglia. The absence of inflammatory cell infiltration in the facial nucleus suggests that neurotactin and CX_3CR1 are parts of an intrinsic cellular response that occurs during motoneurone regeneration[18].

CNS tumours

Many chemokines were first isolated from tumour cell lines and experimental data revealed their paradoxical role in tumourigenicity[4,59]. Tumour cells spontaneously produce chemokines in order to facilitate transendothelial migration of metastasizing cells and to prevent chemotaxis of leukocytes. By contrast, chemokine secretion by tumours (using murine tumour-transduction models) inhibits tumour growth by potentiating monocyte-mediated cell death and increasing macrophage infiltration[60]. Chemokines can also modulate angiogenesis or neovascularization, which is crucial for tumour growth. The ELR-CXC chemokines are potent angionenic factors whereas the non-ELR-CXC chemokines possess angiostatic functions[2,59]. Block of angiogenesis through modulation of chemokine activity is now considered as a therapeutic strategy for the treatment of brain tumours[4,60].

Astrocytomas, glioblastomas and meningiomas have all been shown to express MCP-1 mRNA or protein, and anti-MCP-1 is able to block the chemotactic effect of monocytes induced by tumour fluids of glioblastomas and astrocytomas[61–64]. Moreover, the upregulation of IL-8 (mRNA and protein) by inflammatory stimuli or by reduced microenvironmental oxygen pressure in glioblastoma suggests its role in leukocyte activation, chemotaxis and angiogenesis[65].

Multiple sclerosis

Multiple sclerosis is a human chronic inflammatory and demyelinating disease that induces subsequent neuronal death[66,67]. Although the histopathology of MS is complex and heterogeneous, the lesions are dominated by T cells and macrophage infiltration into the nervous system[66,67]. Recently, acute and chronic-active MS lesions have been shown to be immunoreactive for MCP-1,

MCP-2 and MCP-3 throughout the lesion centre (hypertrophic astrocytes and inflammatory cells) while a strong decrease in immunoreactivity was observed at its edge and only hypertrophic astrocytes were reactive for chemokines outside the lesion[68]. MCP-1 and IL-8 mRNA have also been detected in MS plaques[68,69] and the levels of MIP-1α, IP-10 and RANTES in the cerebrospinal fluid of MS patients are increased over control values[70,71]. The use of animal models such as acute or chronic experimental allergic encephalomyelitis (EAE) in rat or mouse is helpful to understand the role of chemokines in the inflammatory cascade[22,71–73]. Briefly, these studies revealed that the different types of chemokines involved are related spatially and temporally with different inflammatory cells (e.g. MIP-1α and leukocytes, MCP-1 and astrocytes/macrophages, RANTES and T cells) and with the different forms of EAE (MIP-1α levels are correlated with the acute phase and Th1-mediated immune responses while MCP-1 levels correlate with relapsing EAE development and Th2-mediated immune responses). Anti-MIP-1α treatment prevents the development of acute but not relapsing EAE whereas anti-MCP-1 antibodies reduce the severity of relapsing EAE (Ref. 74). Globally, it is likely that the chemokines play a deleterious effect in EAE/MS but further studies are necessary to clarify the respective role of each chemokine in the various phases of the immune response and to establish their action on oligodendrocytes and neurones.

Neurodegenerative diseases

Although CNS inflammation appears to be a common feature of neurodegenerative diseases such as Alzheimer's, Parkinson's and Huntington's diseases, and human immunodeficiency virus (HIV) dementia, only a few studies thus far have investigated the possible role of chemokines in these diseases. The recent findings that some chemokine receptors such as CXCR2, CXCR4 and CCR5 (Refs 11, 13 and 15, respectively) are expressed in the hippocampus and other limbic regions (cf. Table 2) could be taken as an indication of their possible relevance in dementia although data in that regard are currently lacking.

Alzheimer's disease

An upregulation of the CXCR2 protein (receptor for IL-8) occurs in senile plaques adjacent to the hippocampus in the brains of Alzheimer's patients[11]. Because IL-8 is able to promote survival of hippocampal neurones[40], a possible involvement of IL-8/CXCR2 in compensatory and reparative mechanisms in the Alzheimer's brain should be considered. IL-8 mRNA is also known to be regulated by amyloid peptides in human monocytes[75].

HIV dementia

Like most retroviruses, the HIV virus is neurotropic and as a result, various neurological symptoms including motor and cognitive dysfunctions occur in AIDS patients[76]. Progressive atrophies of the striatum, temporal limbic cortex and white matter are observed in HIV patients consistent with the subcortical pattern of neurocognitive dysfunctions. However, brain atrophy and microglial activation with BBB alteration are also seen in asymptomatic-HIV-positive patients[77,78].

At least six chemokine receptors (CXCR4, CCR2b, CCR3, CCR5, CCR8 and CX_3CR1) could be implicated in HIV infection, depending on the HIV strains. In addition to their expression in the immune system, these receptors are known to be expressed by astrocytes, microglia and neurones, or both[14,17,20]. HIV infection of microglia appears to proceed via the use of the CD4 molecule and a chemokine co-receptor (as in immune cells), whereas HIV infection of astrocytes, neurones and oligodendrocytes occurs via a CD4-independent mode[76]. The HIV-1 envelop glycoprotein, like SDF-1, induces neuronal apoptosis via the CXCR4 receptor in human neuronal cell lines[79,80]. Neuronal apoptosis induced by the HIV-1 envelop glycoprotein has also been reported to occur in rat hippocampal neurones[81]. In addition, infected microglia and astrocytes can generate various neurotoxins such as NO, quinolinic acid, arachidonic acid or tumour necrosis factor-α, the latter enhancing viral replication in microglia and the death of oligodendrocytes[76,80]. Elevated expressions of MIP-1α and MIP-1β have also been observed in the brains of patients suffering from AIDS dementia in comparison to tissues from AIDS patients without dementia[82]. The use of antibodies, recombinant chemokines or GAG-binding proteins to block the expression or function of chemokine receptors are under investigation to reduce the infectibility of the HIV virus[6,83].

General conclusions

In addition to their powerful effect on leukocyte infiltration in the brain, it is likely that chemokines also mediate brain inflammation via their upregulation in astrocytes, microglia and circulating lymphocytes. Chemokine expression in neurones seems to be linked to a metabolic dysregulation because only tumour cells synthesize and secrete chemokines. However, neurones can express chemokine receptors, even under physiological conditions, which suggests additional roles (neuronal patterning, apoptosis, survival) for chemokines in the normal functioning of the brain. Reports of exciting data in that regard are just beginning but promise to be the focus of intense research activities for years to come.

Selected references

1 Rollins, B. J. (1997) *Blood* 90, 909–928
2 Luster, A. D. (1998) *New Engl. J. Med.* 338, 436–445
3 Wells, T. N. C., Power, C. A. and Proudfoot, A. E. I. (1998) *Trends Pharmacol. Sci.* 19, 376–380
4 Schall, T. J. (1994) in *The Cytokine Handbook* (Thomson, A., ed.), pp. 419–560, Academic Press
5 Murphy, P. M. (1996) *Cytokine Growth Factor Rev.* 7, 47–64
6 McFadden, G. and Kelvin, D. (1997) *Biochem. Pharmacol.* 54, 1271–1280
7 Horuk, R. (1994) *Trends Pharmacol. Sci.* 15, 159–165
8 Ehrlich, L. C. *et al.* (1998) *J. Immunol.* 160, 1944–1948
9 Lacy, M. *et al.* (1995) *J. Neuroimmunol.* 61, 71–78

10 Halks-Miller, M., Hesselgesser, J., Miko, I. J. and Horuk, R. (1997) *Methods Enzymol.* 288, 27–38
11 Horuk, R. *et al.* (1997) *J. Immunol.* 158, 2882–2890
12 Hesselgesser, J. *et al.* (1997) *Curr. Biol.* 7, 112–121
13 Lavi, E. *et al.* (1997) *Am. J. Pathol.* 151, 1035–1042
14 He, J. *et al.* (1997) *Nature* 385, 645–649
15 McManus, C. M., Brosnan, C. F. and Berman, J. W. (1998) *J. Immunol.* 160, 1449–1455
16 Tanabe, S. *et al.* (1997) *J. Neurosci.* 17, 6522–6528
17 Rottman, J. B., Ganley, K. P., Williams, K., Lu, L., Mackay, C. R. and Ringler, D. J. (1997) *Am. J. Pathol.* 151, 1341–1350
18 Harrison, J. K. *et al.* (1998) *Proc. Natl. Acad. Sci. U. S. A.* 95, 10896–10901
19 Bazan, J. F. *et al.* (1997) *Nature* 385, 640–644
20 Pan Y. *et al.* (1997) *Nature* 387, 611–617
21 Horuk, R. *et al.* (1996) *J. Leukocyte Biol.* 59, 29–38
22 Ransohoff, R. M., Glabinski, A. and Tani, M. (1996) *Cytokine Growth Factor Rev.* 7, 35–46
23 Baggiolini, M. (1998) *Nature* 392, 565–568
24 Springer, T. A. (1994) *Cell* 76, 301–314
25 Bell, M. D., Taub, D. D. and Perry, V. H. (1996) *Neuroscience* 74, 283–292
26 Lira, S. A., Fuentes, M. E., Strieter, R. M. and Durham, S. K. (1997) *Methods Enzymol.* 287, 304–318
27 Tani, M. *et al.* (1996) *J. Clin. Invest.* 98, 529–539
28 Boring, L. *et al.* (1997) *J. Clin. Invest.* 100, 2552–2561
29 Cacalano, G. *et al.* (1994) *Science* 265, 682–684
30 Cook, D. N. *et al.* (1995) *Science* 269, 1583–1585
31 Gao, J. L. *et al.* (1997) *J. Exp. Med.* 185, 1959–1968
32 Lu, B. *et al.* (1998) *J. Exp. Med.* 187, 601–608
33 Rothenberg, M. E., MacLean, J. A., Pearlman, E., Luster, A. D. and Leder, P. (1997) *J. Exp. Med.* 185, 785–790
34 Zhou, Y. *et al.* (1998) *J. Immunol.* 160, 4018–4025
35 Nagasawa, T. *et al.* (1996) *Nature* 382, 635–638
36 Tachibana, K. *et al.* (1998) *Nature* 393, 591–594
37 Zou, Y-R., Kottmann, A. H., Kuroda, M., Taniuchi, I. and Littman, D. R. (1998) *Nature* 393, 595–599
38 Jazin, E. E., Soderstrom, S., Ebendal, T. and Larhammar, D. (1997) *J. Neuroimmunol.* 79, 148–154
39 Mehler, M. F. and Kessler, J. A. (1997) *Trends Neurosci.* 20, 357–365
40 Araujo, D. M. and Cotman, C. W. (1993) *Brain Res.* 600, 49–55
41 Bolin, L. M. *et al.* (1997) *J. Immunol.* 81, 49–57
42 Heesen, M. *et al.* (1996) *J. Neurosci. Res.* 45, 382–391
43 Hayashi, M., Luo, Y., Laning, J., Strieter, R. M. and Dorf, M. E. (1995) *J. Neuroimmunol.* 60, 143–150
44 Martiney, J. A., Cuff, C., Litwak, M., Berman, J. and Brosnan, C. F. (1998) *Neurochem. Res.* 23, 349–359
45 Perry, V. H., Bell, M. D., Brown, H. C. and Matyszak, M. K. (1995) *Curr. Opin. Neurobiol.* 5, 636–641
46 Smith, G. L. (1996) *Curr. Opin. Immunol.* 8, 467–471
47 Wells, T. N. and Schwartz, T. W. (1997) *Curr. Opin. Biotechnol.* 8, 741–748
48 Ransohoff, R. M. and Tani, M. (1998) *Trends Neurosci.* 21, 154–159
49 Liu, T. *et al.* (1993) *Neurosci. Lett.* 164, 125–128
50 Wang, X., Yue, T., Barone, F. C. and Feuerstein, G. Z. (1995) *Stroke* 26, 661–666
51 Gourmala, N. G., Buttini, M., Limonta, S., Sauter, A. and Boddeke, H. W. (1997) *J. Neuroimmunol.* 74, 35–44
52 Matsumoto, T. *et al.* (1997) *Lab. Invest.* 77, 119–125
53 Kostulas, N. *et al.* (1998) *Stroke* 29, 462–466
54 Feuerstein, G. Z., Wang, X. and Barone, F. C. (1997) *Ann. New York Acad. Sci.* 825, 179–193
55 Ghirnikar, R. S., Lee, Y. L. and Eng, L. F. (1998) *Neurochem. Res.* 23, 329–340
56 Hausmann, E. H. S. *et al.* (1998) *Brain. Res.* 788, 49–59
57 Glabinski, A. R., Tani, M., Balasingam, V., Yong, V. W. and Ransohoff, R. M. (1996) *J. Immunol.* 156, 4363–4368
58 McTigue, D. M. *et al.* (1998) *J. Neurosci. Res.* 53, 368–376
59 Strieter, R. M., Polverini, P. J., Arenberg, D. A. and Kunkel, S. L. (1995) *Shock* 4, 155–160
60 Nakashima, E. *et al.* (1996) *Pharm. Res.* 13, 1896–1901
61 Desbaillets, I. *et al.* (1994) *Int. J. Cancer* 58, 240–247
62 Leung, S. Y., Wong, M. P., Chung, L. P., Chan, A. S. and Yuen, S. T. (1997) *Acta Neuropathol.* 93, 518–527
63 Sato, K., Takeshima, H., Yoshimura, T. and Ushio, Y. (1995) *J. Neurosurg.* 82, 874–878
64 Takeshima, H., Kuratsu, J., Takeya, M., Yoshimura, T. and Ushio, Y. (1994) *J. Neurosurg.* 80, 1056–1062
65 Desbaillets, I., Diserens, A. C., Tribolet, N., Hamou, M. F. and Van Meir, E. G. (1997) *J. Exp. Med.* 186, 1201–1212
66 Amor, S., Baker, D., Layward, L., McCormack, K. and van Noort, J. M. (1997) *Immunol. Today* 18, 368–371
67 Lucchinetti, C. F., Bruck, W., Rodriguez, M. and Lassmann, H. (1996) *Brain Pathol.* 6, 259–274
68 McManus, C. *et al.* (1998) *J. Immunol.* 86, 20–29
69 Schluesener, H. J. and Meyermann, R. (1993) *Acta Neuropathol.* 86, 393–396
70 Miyagishi, R., Kikuchi, S., Fukazawa, T. and Tashiro, K. (1995) *J. Neurol. Sci.* 129, 223–227
71 Karpus, W. J. and Ransohoff, R. M. (1998) *J. Immunol.* 161, 2667–2671
72 Eng, F. L., Ghirnikar, R. S. and Lee, Y. L. (1996) *Neurochem. Res.* 21, 511–525
73 Glabinski, A. R., Tani, M., Strieter, R. M., Tuohy, V. K. and Ransohoff, R. M. (1997) *Am. J. Pathol.* 150, 617–630
74 Karpus, W. J. and Kennedy, K. J. (1997) *J. Leukocyte Biol.* 62, 681–687
75 Meda, L. *et al.* (1995) *J. Neuroimmunol.* 59, 29–33
76 Kolson, D. L., Lavi, E. and Gonzalez-Scarano, F. (1998). *Adv. Virus Res.* 50, 1–50
77 Sinclair, E., Gray, F., Ciardi, A. and Scaravilli, F. (1994) *J. Neuropathol. Exp. Neurol.* 53, 43–50
78 Stout, J. C. *et al.* (1998) *Arch. Neurol.* 55, 161–168
79 Hesselgesser, J. *et al.* (1998) *Curr. Biol.* 8, 595–598
80 Dubois-Dalcq, M., Altmeyer, R., Chiron, M. and Wilt, S. (1995) *Curr. Opin. Neurobiol.* 5, 647–655
81 Aggoun-Zouaoui, D. *et al.* (1996) *NeuroReport* 7, 433–436
82 Schmidtmayerova, H. *et al.* (1996) *Proc. Natl. Acad. Sci. U. S. A.* 93, 700–704
83 Cairns, J. S. and D'Souza, M. P. (1998) *Nat. Med.* 4, 565–568

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