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Neuronal Chemokines: Versatile Messengers In Central Nervous System Cell Interaction

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Abstract Whereas chemokines are well known for their ability to induce cell migration, only recently it became evident that chemokines also control a variety of other cell functions and are versatile messengers in the interaction between a diversity of cell types. In the central nervous system (CNS), chemokines are generally found under both physiological and pathological conditions. Whereas many reports describe chemokine expression in astrocytes and microglia and their role in the migration of leukocytes into the CNS, only few studies describe chemokine expression in neurons. Nevertheless, the expression of neuronal chemokines and the corresponding chemokine receptors in CNS cells under physiological and pathological conditions indicates that neuronal chemokines contribute to CNS cell interaction. In this study, we review recent studies describing neuronal chemokine expression and discuss potential roles of neuronal chemokines in neuron–astrocyte, neuron–microglia, and neuron–neuron interaction.

Keywords CNS · Central nervous system · Neurons · Astrocytes · Microglia · Chemokines · Cell interaction

Introduction

Chemokines are small proteins that are able to induce a chemotactic response in cells expressing the corresponding chemokine receptors. Since the discovery of the first protein with chemotactic activity [1], the chemokine family has expanded to approximately 50 chemokines [2] and 20 receptors [3]. Chemokines have been divided into four groups based on the position of four conserved cysteine residues in the N-terminal region of the protein. The two largest groups are CXC and CC. The first two cysteines in the CXC group are separated by one amino acid residue, whereas the first two cysteines in the CC group are adjacent to each other [4, 5]. The two small groups are the C chemokines, with only one cysteine in the N-terminal region, and the CX3C chemokine, where the first two cysteines are separated by three amino acid residues [5]. Chemokine receptors are designated according to the chemokine group they preferentially bind. For example, CC chemokines bind to CC receptors and so on. There has yet only been one exception reported, namely CCL21, that, in addition to CCR7, also binds to CXCR3 [6–8]. All chemokine receptors belong to the family of G-protein coupled receptors (GPCRs). In general, GPCRs can bind many different G-proteins, allowing for a great variety of intracellular signaling pathways (for excellent review, see [9]). The majority of chemokine-induced responses are inhibited by *pertussis toxin* (PTX), indicating that $G_{\alpha i}$−proteins mediate many effects [10]. Chemokine receptors can activate intracellular targets like adenylcyclase, phospholipases, GTPases like Rho, Rac, and Cdc42 and pathways of major kinases like mitogen-activated protein kinase (MAPK) and phosphatidyl inositol-3 kinase (PI3-K) [11, 12]. This diversity of intracellular signaling shows that chemokine receptors, in addition to pathways involved in cell migration, also activate other pathways and may, in that way, control a great spectrum of cellular functions [13, 14].

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Chemokines are well-known regulators of peripheral immune cell trafficking under both physiological and pathological conditions (reviewed by [15–17]). In addition to chemo-attraction of immune cells, chemokines have been implicated in a variety of cell functions, such as early development, formation of secondary lymphoid organs, wound healing, angiogenesis and angiostasis, regulation of adhesion molecule expression, development of Th1/Th2 profiles, tumor growth, and metastasis [5, 14, 18–24]. Thus, from being molecules thought to solely orchestrate immune cell migration, chemokines are now considered versatile messengers with the ability to control the interaction between a wide diversity of cell types.

In addition to their presence in the periphery, numerous studies have demonstrated that chemokines are also expressed in the central nervous system (CNS), where they play a crucial role in physiological and pathological conditions, such as development, synaptic transmission, homeostasis, injury, and disease-associated neuroinflammation [19, 25, 26]. Although astrocytes and microglia are the primary source of chemokines, there is evidence that neurons express and secrete chemokines as well, indicative of a neuronal contribution to chemokine signaling. In this paper, we review recent studies describing neuronal chemokine expression and discuss the potential roles of neuronal chemokines in neuron–astrocyte, neuron–microglia, and neuron–neuron interaction.

Neuronal Chemokine Expression

Approximately 60 studies describe chemokine expression in neurons under physiological and pathological conditions (see Table 1). These studies, of which the majority is published in the last 3 years, are reviewed in the following sections.

CC Chemokines

CCL2

CCL2 is currently the most extensively described neuronal chemokine. The majority of reports describing neuronal CCL2 expression are focused on pathological conditions. An induction of neuronal CCL2 expression was described upon ischemia [27–29], after axonal injury [30–34] and in motoneurons of patients with amyotrophic lateral sclerosis (ALS), and in mouse models for ALS [35, 36]. Interestingly, neuronal CCL2 expression in response to ischemia was detectable within 2 h, whereas CCL2 expression in astrocytes was detected only after 2 days [27]. Although most reports show induction of neuronal CCL2 expression under pathological conditions, a recent study has shown constitutive CCL2 expression in neurons throughout the rat brain [37]. This study demonstrated that, depending on the brain region, up to 100% of the neurons were positive for CCL2 [37]. CCL2 was mainly detected in neuronal cell bodies and costaining-depicted colocalization with various neurotransmitters and neuropeptides, corroborating a population-specific expression of CCL2 [37]. Constitutive neuronal CCL2 expression was also shown in a human neuronal cell line [38] and during human CNS development [39].

CCL3, CCL4, and CCL5

At present, there is only one study describing neuronal CCL3 expression in situ, depicting protein expression in adult human brain [40]. Further, expression of CCL3, CCL4, and CCL5 was described in cultured forebrain neurons derived from human first trimester embryos. These chemokines showed increased expression after exposure to immunological stimuli [41]. CCL3 and CCL4 expression were induced in mouse cerebellar granule neurons after infection with *Toxoplasma gondii* [42], as was CCL5 expression after viral infections [43, 44].

CCL21

In a middle cerebral artery occlusion (MCAO) mouse model of brain ischemia, cortical neurons rapidly expressed CCL21 in the penumbra of the ischemic core. Because control brain tissue did not express CCL21, CCL21 was assumed to be specifically expressed in endangered neurons [45]. In accordance with the in vivo findings, CCL21 expression was induced in cortical neurons in vitro within 2 h after excitotoxicity [45, 46]. The CCL21 expression in endangered neurons was rather surprising, as CCL21 is well known for its constitutive expression in secondary lymphoid organs, controlling the homing of mature dendritic cells and naïve T cells [47] and is, therefore, generally considered a homeostatic chemokine linked to the development and maintenance of secondary lymphoid organs [48]. The rapid CCL21 expression in endangered neurons after injury indicates a brain specific role of CCL21. This assumption is corroborated by findings in transgenic mice in which CCL21 was expressed ectopically in various tissues. CCL21 expression in the brain induced a massive brain inflammation that killed the animals within 3 days after the expression onset [49], whereas CCL21 expression in the skin induced the formation of secondary lymphoid structures [50].

Other CC Chemokines

A single study has demonstrated a constitutive and inducible expression of CCL20 in rat cerebellar granule

Table 1 Neuronal chemokine expression

Chemokine	Species	Condition	RNA	Protein	References
CCL2	h	Brain		+	[39]
		Spinal cord, ALS		↑	[35]
		Monoculture	↑	+	[41]
		Cell line		+	[38]
	r	Brain		+	[37]
		Brain, cranial nerve injury	↑	↑	[30]
		Brain, ischemia	↑	↑	[28]
		Retina, ischemia	↑		[168]
		Spinal cord, peripheral nerve injury	↑	↑	[31–34]
		Monoculture		+	[164]
	m	Brain, ischemia		↑	[27, 29]
		Spinal cord, ALS model		↑	[36]
		Monoculture, West Nile virus	↑		[43]
CCL3	h	Brain, AD		≈	[40]
		Monoculture	↑	+	[41]
	r	Retina, ischemia	↑		[168]
		Monoculture		+	[51]
	m	Monoculture		↑	[42]
CCL4	h	Monoculture	↑	+	[41]
	r	Retina, ischemia	↑		[168]
	m	Monoculture		↑	[42]
CCL5	h	Monoculture	↑	+	[41]
	m	Monoculture	↑	↑	[43, 44]
CCL20	r	Monoculture		+/↑	[51]
		Trigeminal neuron culture	↓		[169]
CCL21	m	Brain, ischemia	↑		[45]
		Monoculture	↑	↑	[45, 46]
		Neonatal hippocampal slice culture		↑	[46]
CXCL1/2/3	r	Monoculture	+	+	[51]
CXCL8	h	Monoculture	+		[41]
CXCL9	m	Monoculture	+		[43]
CXCL10	h	Brain, HIV		↑	[54]
		Mixed brain culture		+	[54]
	mac	Brain, HIV		↑	[54]
	r	Brain, ischemia		↑	[52]
	m	Brain, entorhinal cortex lesion		↑	[53]
		Brain, West Nile virus	↑	↑	[43]
		Monoculture	+	+	[43]
CXCL11	m	Monoculture	+		[43]
CXCL12	h	Brain, HIV		↑	[59]
		Monoculture		+	[59]
	r	Brain	+	+	[55, 60–62]
		Monoculture	+	+	[58, 60, 87]
	m	Brain, ischemia	≈/↓		[56]
		Brain, LPS injection	≈		[56]
		Mixed brain culture		+	[59]
CX3CL1	h	Brain, MS		↑	[113]
		Brain, HIV		↑	[170]
		Spinal cord		+	[66]
		Monoculture	≈	≈/↑/↓	[74, 75, 138]
		Cell line	≈	↑/↓[a]	[66, 75, 138]
	mac	Brain		+	[66]
	r	Brain and spinal cord, EAE	≈		[63, 65, 66, 68]
		Spinal cord, peripheral nerve injury	≈	≈	[171, 172]
		Brain, LPS injection		≈	[67]
		Brain, KA injection		≈	[67]

Table 1 (continued)

Chemokine	Species	Condition	RNA	Protein	References
		Monoculture	≈	↑/↓[a]	[64, 65, 73, 76, 78, 118]
	m	Brain	+	+	[69]
		Brain, prion disease		≈	[67]
		Brain, LPS injection		≈	[67]
		Brain, KA injection		≈	[67]
		Brain, EAE	≈		[66]
		Monoculture	≈	≈	[77]
		Cell line	≈	≈	[77]

h Human, *mac* macaque, *r* rat, *m* mouse, *ALS* amyotrophic lateral sclerosis, *AD* Alzheimer's disease, *HIV* human immunodeficiency virus, *MS* multiple sclerosis, *EAE* experimental autoimmune encephalomyelitis, *LPS* lipopolysaccharide, *KA* kanaic acid; + present, ≈ present without change in mentioned conditions, ↑ present with increase in mentioned conditions, ↓ present with decrease in mentioned conditions,
[a] Increase in soluble CX3CL1 and decrease in membrane-bound CX3CL1

neurons in vitro, which was suggested to play a role in neuronal apoptosis [51]. Expression of other CC chemokines has not yet been observed in neurons.

CXC Chemokines

CXCL10

CXCL10 expression was first described in cortical neurons in rat in response to MCAO-induced brain ischemia [52]. Remarkably, neuronal CXCL10 expression was transient and appeared rapidly after stroke (within 3–12 h), whereas CXCL10 expression in astrocytes was detectable later and persisted up to 15 days after MCAO [52]. Correspondingly, neurons also showed a rapid CXCL10 expression after entorhinal cortex lesion [53]. Further, neuronal CXCL10 expression and release was induced after viral infection in vitro and in vivo [43, 54].

CXCL12

The CXCL12 gene contains three splice variants, termed stromal cell-derived factor-1 (SDF-1) α, β, and γ. SDF-1γ was cloned from rat brain and showed constitutive neuronal mRNA expression with almost no change in level after peripheral nerve injury [55]. In addition, SDF-1α showed neuronal mRNA expression with almost no change in level after brain ischemia or intracerebral LPS injection [56]. In contrast, SDF-1 β mRNA expression was not detected in neurons [56]. As little is known about the role of SDF splice variants, and most studies did not specify the splice variants, CXCL12 is used for all SDF splice variants henceforth.

Like CCL2, but in contrast to most of the other neuronal chemokines, CXCL12 is expressed constitutively in specific neuronal populations. Neuronal CXCL12 expression in vitro was observed in cultured cortical, hippocampal, and cerebellar neurons from human, rat, and mouse [57–60]. Neuronal CXCL12 expression in vivo was studied in detail in the adult rat brain, showing CXCL12 mRNA and protein expression in cholinergic, dopaminergic, and vasopressin containing neurons throughout the brain [61, 62].

Other CXC Chemokines

Studies describing the expression of other CXC chemokines in neurons are limited. Most notably, in vitro neuronal mRNA expression of CXCL1 [51], CXCL8 [41], CXCL9, and CXCL11 [43] has been illustrated. Expression of other CXC chemokines has not yet been described in neurons.

CX3CL1

CX3CL1 was the first chemokine shown to be expressed in neurons [63–66]. Because microglia were shown to express the corresponding receptor CX3CR1, a role of CX3CL1–CX3CR1 signaling in neuron–microglia interaction was suggested [63–65]. CX3CL1 is constitutively expressed in human, macaque, rat, and mouse neurons in vitro and in vivo, with high expression in cerebral cortex, hippocampus, caudate putamen, thalamus, and olfactory bulb [63, 65, 66, 68, 69]. CX3CL1 appears to be the only chemokine with a higher expression level in brain than in peripheral organs [70]. It is membrane bound and can be cleaved from the cell surface by proteases of the A Disintegrin and Metalloprotease (ADAM) family [71, 72]. The neuronal CX3CL1 mRNA expression remained relatively stable in response to both neuron-damaging stimuli in vitro [73–77] and during neuroinflammation in vivo [66], whereas in vitro neurons released CX3CL1 protein after glutamate-induced damage [73, 74, 78]. Furthermore, CX3CL1 concentrations higher than 300 pg/mg were described in aqueous extracts of the brain [79], indicating that CX3CL1 can be cleaved from the neuronal membrane and released

into the extracellular environment. It is yet unknown which ADAM protease cleaves CX3CL1 in neurons and whether CX3CL1 protein expression changes during in vivo neuroinflammation or degeneration.

Potential Roles of Neuronal Chemokines in Neuron–Astrocyte, Neuron–Microglia, and Neuron–Neuron Interaction

Astrocytes, microglia, and neurons have been shown to express chemokine receptors in vitro under physiological and pathological conditions and in vivo. These would include CCR2 for CCL2, CXCR3 for CCL21 and CXCL10, CXCR4 for CXCL12, and CX3CR1 for CX3CL1. Studies describing the expression of these chemokine receptors on astrocytes, microglia, and neurons (see Table 2) and studies indicating a role for these chemokine–chemokine receptor pairs in CNS cell interaction are discussed in the following sections on neuron–astrocyte, neuron–microglia, and neuron–neuron interaction.

Neuron–Astrocyte Interaction

Astrocytes comprise the largest group of CNS-residing cells and are not only essential in development, homeostasis, maintenance of the blood–brain barrier, and regulation of central blood flow but are also involved in the immune defense of the CNS. Furthermore, astrocytes are considered to be involved in neuronal information processing [80].

It is becoming clear that astrocytes play an active role in the intricate chemokine network of the CNS. Not only has it been shown that astrocytes express a wide variety of constitutive and inducible chemokines in vivo and in vitro, there is also extensive evidence that they express a repertoire of chemokine receptors under physiological and pathological conditions (see reviews [81, 82]).

Neuronal Chemokines Induce Calcium Transients in Astrocytes

The activation of intracellular calcium transients is a hallmark in chemokine receptor signaling, a mechanism that also holds true for astrocytes [57, 76, 83–86]. Activation of GPCRs, including chemokine receptors, results in a rapid release of calcium from the endoplasmatic reticulum (ER) through the activation of inositol-1,4,5-triphosphate receptors on the ER membrane. One of the first chemokines described to induce calcium transients in astrocytes is CXCL12 [57, 85–87]. CXCL12 concentrations ranging from 0.1 to 100 ng/ml [85, 86] or 10–100 nM [57, 87] induced calcium fluxes in in vitro human, rat, and mouse astrocytes. In all cases, CXCL12-induced calcium mobilization was PTX-sensitive, indicating that this process is $G\alpha_i$-protein mediated. Similar results were found for CXCL10 [84], CCL2 [83, 88], and CX3CL1 [76].

In astrocytes, intracellular calcium transients not only function as a second messenger in multiple intracellular signaling pathways but are also implicated in astrocyte–astrocyte signal propagation, astrocyte–neuron synaptic transmission, and neurotransmitter release (see reviews [80, 89]). Recent findings corroborate that chemokines could also be involved in astrocyte-mediated neurotransmitter release. CXCL12 induced calcium-dependent release of glutamate from astrocytes in human and rat astrocyte cultures and rat hippocampal slice cultures [90]. Moreover, reports that investigated the effects of CXCL12 on the electrophysiological properties of neurons in brain slice cultures suggest that CXCL12-induced effects on neurons at least partly depend on astrocytic glutamate release [91–93]. Whether this astrocytic glutamate release was induced by CXCR4 activation or via other pathways was not investigated.

Neuronal Chemokines Induce Astrocyte Proliferation and Migration in Vitro: Implications for Astrogliosis?

Astrocytes respond to CNS injury or neuroinflammation by enhanced GFAP expression, proliferation, and possibly, migration, a process known as astrogliosis (see review [94]). In these reactive astrocytes, enhanced expression of chemokine receptors has been described under various pathological conditions, such as multiple sclerosis (MS), human immunodeficiency virus (HIV) infection, ischemia, and neoplasm [95–97]. Under these conditions, CXCR3 was mainly found in reactive astrocytes in the proximity of the lesion sites, suggesting that induction of CXCR3 expression in astrocytes is limited to damaged areas of the brain [95–97]. A comparable induction of CCR2 expression was found in reactive astrocytes in MS patients [97].

Interestingly, both CCL2 and CXCL10 are implicated in astrocyte proliferation in vitro [98, 99]. In addition, CXCL12 has been shown to induce astrocyte proliferation in vitro, a process that is dependent on activation of extracellular signal-regulated kinases ERK1 and ERK2 [87, 100–102]. Both CXCL12-induced astrocyte proliferation and ERK1/2 activation was inhibited by PTX and wortmannin, suggesting that they are dependent on upstream activation of $G\alpha_i$ proteins and PI3-K [87].

As chemokines are primarily known for their capacity to induce cell migration, migration assays have been used to determine chemokine receptor functionality in astrocytes [103]. Accordingly, astrocyte migration was demonstrated in vitro in response to CCL2, CXCL10, and CXCL12 [83, 84, 86, 103, 104]. Thus, reactive astrocytes express various chemokine receptors and activation of these receptors in

Table 2 Chemokine receptor expression in astrocytes, microglia, and neurons

Chemokine	Receptor	Cell type	Species	Condition	RNA	Protein	References
CCL2	CCR2	astrocyte	h	Brain, MS, HIV		↑	[96, 97, 173]
				Monoculture	↑	↑	[83, 99, 174–176]
			mac	Monoculture	↑		[175]
			r	Brain, EAE, LPS injection		↑	[177, 178]
		microglia	h	Brain, MS, HIV		↑	[96, 173, 179]
				Monoculture	↓	+	[173, 180]
				Glia culture		+	[99]
			r	Brain, tumor, LPS injection, NMDA injection		↑	[177, 181, 182]
				Monoculture	↑		[88]
			m	Spinal cord, peripheral nerve injury		↑	[183]
		neuron	h	Brain, HIV		+	[184]
				Monoculture	+	+	[38]
				Cell line	+	+	[38]
			r	Brain and spinal cord	+	+	[161, 177, 185]
				Monoculture	+	+	[161, 164]
CXCL10/ CCL21	CXCR3	astrocyte	h	Brain, MS, HIV		↑	[95, 97, 179, 186]
				Astrocyte culture	↑	↑	[84, 98, 175]
				Mixed glial culture		+	[95]
			mac	Monoculture		+	[175]
			m	Monoculture		+	[84]
		microglia	h	Monoculture	+	+	[7, 84, 98, 114]
				Cell line	↑	↑	[98]
			r	Cell line	↑/↓		[187]
			m	Brain, various infectious agents, axotomy	≈/↑	≈/↑	[125]
				Monoculture	+	↓	[45, 84]
				Cell line	↑/↓		[188]
		neuron	h	Brain, AD	+	≈	[95, 179, 189]
				Monoculture	+	+	[38]
				Cell line	+	+	[38]
			mac	Brain, HIV		+	[54]
			r	Monoculture		+	[163]
CXCL12	CXCR4	astrocyte	h	Brain, HIV		↑	[173, 190, 191]
				Monoculture	↑	↑	[85, 90, 98, 99, 175, 192–196]
			mac	Monoculture	↑	↑	[85, 175]
			r	Brain		+	[197]
				Monoculture	↑/↓	↑/↓	[57, 58, 102, 198]
			m	Monoculture	↑/↓	↑/↓	[86, 101, 104, 199, 200]
		microglia	h	Brain and spinal cord, HIV	+	+	[173, 179, 190, 191, 201, 202]
				Monoculture	+	↓	[98, 99, 191, 202–205]
				Cell line		≈	[98]
			bab	Monoculture	↑		[206]
			r	Brain		+	[197]
				Monoculture	≈/↑	+	[58, 207, 198]
			m	Cell line	+		[86]
		neuron	h	Brain, HIV	+	≈/↑	[179, 184, 191, 197, 202, 204, 208]
				Monoculture	+	+	[38, 85]
				Mixed brain culture	+	+	[202]
				Cell line	+	+	[38, 191, 209]
			mac	Brain		+	[210, 211]
				Monoculture		+	[85]
			r	Brain	+	+	[57]
				Monoculture	+	+	[64, 158]

Table 2 (continued)

Chemokine	Receptor	Cell type	Species	Condition	RNA	Protein	References
CX3CL1	CX3CR1	astrocyte	h	Brain, MS		≈	[113]
				Monoculture	↑	+	[113, 175]
			mac	Monoculture	↑		[175]
			r	Monoculture	≈/↑	↑	[76, 198, 212]
			m	Monoculture	↓	↓	[77, 81, 200]
		microglia	h	Brain, MS		≈	[113]
				Brain, HIV		↑	[170]
				Monoculture	+	+	[75, 113]
			r	Brain, ischemia, prion disease, cranial nerve injury, EAE	↑	↑	[63, 67, 68, 213]
				Brain, LPS injection, KA injection		≈	[67]
				Spinal cord, peripheral nerve injury	↑	↑	[171, 172]
				Monoculture	↑/↓	↑	[63, 65, 198, 212, 214]
				Cell line	↓		[187]
				Brain, LPS injection, KA injection		≈	[67]
			m	Monoculture	≈	≈	[77]
		neuron	h	Monoculture	+	+	[75]
				Cell line	≈	↑	[75]
			r	Brain, LPS injection, KA injection		≈	[67]
				Monoculture	+	+	[64, 139]
			m	Brain, prion disease		↓	[67]
				Brain, LPS injection, KA injection		≈	[67]

h human, *mac* macaque, *bab* baboon, *r* rat, *m* mouse, *MS* multiple sclerosis, *HIV* human immunodeficiency virus, *EAE* experimental autoimmune encephalomyelitis, *LPS* lipopolysaccharide, *NMDA* *N*-methyl-D-aspartatic acid, *AD* Alzheimer's disease, *KA* kainic acid; + present, ≈ present without change in mentioned conditions, ↑ present with increase in mentioned conditions, ↓ present with decrease in mentioned conditions

vitro induces proliferation and migration, cellular reactions that are generally involved in astrogliosis. Therefore, it is tempting to speculate that chemokines are involved in the regulation of astrogliosis upon CNS injury or neuroinflammation. Whether neuronal chemokines are indeed responsible for either proliferation or migration of astrocytes in vivo is yet unknown.

Neuron–Microglia Interaction

Microglia in the healthy CNS are ramified cells that continually survey their environment by moving their processes. Upon injury, they quickly protrude their processes toward the damaged site and subsequently transform into amoeboid cells, reflecting a fast activation [105, 106]. Activated microglia form a first line of defense in CNS injury through their capacity to migrate, proliferate, secrete inflammatory and neurotrophic factors, phagocytose-damaged cells and debris, and present antigens [82, 107]. Although activated microglia were initially considered to be detrimental in CNS injury, recent findings indicate a prominent neuroprotective activity as well, suggesting a balance between neurotoxic and neuroprotective microglia activity (see for recent review, [108]). Therefore, it is of particular interest to gain insight into the process of microglia activation. Until now, it is largely unknown which environmental signals mediate microglia surveillance and activation. Almost 10 years ago, chemokines were indicated as promising candidates for neuron–microglia signaling [63–65]. Because then, various studies have described constitutive chemokine expression in neurons and rapid changes in expression levels upon injury. Parallel to this, corresponding chemokine receptors were described in resting and/or activated microglia. In addition, there is increasing evidence that neurons play an important role in microglia activity, which is at least partly mediated by chemokines.

Microglia Activity Upon Neuronal Damage

Upon CNS injury, activated microglia retract their protrusions, transforming into amoeboid cells with migratory and/or proliferative capacities [109–111]. It is known that damaged neurons are accompanied by prominent activated microglia within hours after injury, suggesting that neurons emit signals that attract microglia [111]. Several findings support the notion that these signals are primarily chemokines. Microglia express various chemokine receptors, and cell migration is induced upon exposure to chemokines in vitro [7, 45, 84, 112–115]. Moreover, damaged neurons in culture express and release chemokines like CX3CL1 [73, 74, 78], CCL21 [45, 46], and CXCL10 [43, 54], all of

which are able to induce microglia migration [7, 45, 46, 73, 76, 84, 113, 115]. In accordance with this, inhibition of chemokine function diminished microglia migration in response to supernatants from damaged neurons [73]. Thus, in vitro results suggest a role of neuronal chemokines in neuron–microglia activation.

The issue of chemokine-mediated neuron–microglia activation has been further investigated using genetically modified mice. Mice deficient for either CX3CR1 [116] and CX3CL1 [117] have been studied in various CNS injury and neuroinflammation models. Although CX3CR1 deficiency did not influence microglia activity in response to facial nerve lesion [116], CX3CR1 deficiency was uniformly associated with higher levels of microglia activity in LPS-induced neuroinflammation, 1-Methyl-4-phenyl-1,2,3, 6-tetrahydropyridin-induced neurotoxicity, and in the $SOD1^{G93A}$-model of motoneuronal death in the spinal cord [79]. Interestingly, enhanced microglia activity in the last three models was accompanied by increased neuronal death, indicating that, in wild-type mice, neurotoxic microglia activity is inhibited by CX3CL1–CX3CR1 signaling [79]. These findings are corroborated by several in vitro findings. Exposure of a neuron–microglia coculture to CX3CL1 reduced inflammation-related neuronal death, accompanied by suppressed nitric oxide and proinflammatory cytokine production [118]. In conjunction with these findings, inhibition of endogenous CX3CL1 increased neuronal cell death in cocultures [77]. Moreover, in vitro exposure to CX3CL1 supported microglia survival under basal culture conditions and reduced Fas-ligand induced apoptosis considerably [119]. Thus, exposure of microglia to CX3CL1 reduced microglia toxicity and protected microglia from apoptosis under inflammatory conditions. In contrast to these results, CX3CL1 deficiency reduced the infarct volume and mortality after transient focal cerebral ischemia [117]. However, microglia activity in CX3CL1-deficient and wild-type mice was not compared in this study, making it difficult to determine whether disturbed neuron–microglia signaling was responsible for the differences [117].

Increased microglia toxicity by CXCR3 and its ligands CXCL10 and/or CCL21 is suggested by findings derived from the entorhinal cortex lesion (ECL) model, in which CXCR3 deficiency was associated with reduced microglia activity and reduced loss of secondary neurons in the hippocampal formation [53]. An interesting aspect of chemokines in neuron–microglia signaling is acknowledged in the ECL model. In this paper, microglia activity is specifically found within the midmolecular layer of the dentate gyrus, which is the projection site of the transected neurons (see for review, [120]). The microglia activity at a site distant from the primary lesion indicates transport of the chemokine signal. Recent data reinforced this notion, showing that CCL2 that was induced in dorsal root ganglion (DRG) neurons after peripheral nerve injury was transported to afferent terminals in the spinal cord [34]. Moreover, in vitro neuronal CCL21 was sorted into vesicles, transported into neuronal processes, and even reached presynaptic terminals [46]. The finding of CCL21 protein in neuronal vesicles is a strong indication that neuronal chemokines may be the signals responsible for microglia activity at sites distant from the primary lesion, a phenomenon that has been observed also in humans [121, 122].

A role of CCL2 in microglia activity after neuronal death is suggested by a delayed microglia activity in the thalamus of CCL2-deficient mice in response to cortical injury [123]. The delayed microglia activity was accompanied by a transient improvement of neuron survival in the thalamus, which may indicate that CCL2 is involved in neurotoxic microglia activity [123]. However, it is not yet clear if this effect is due to disturbed neuron–microglia interaction. Damaged neurons are capable to express CCL2, as was found after axotomy in sympathetic ganglia [31] and facial nerve lesion [30], but cortical injury predominantly induced CCL2 mRNA expression in astrocytes [124]. Whether interference with CCL2 signaling would affect microglia activity in the first two models has not yet been investigated.

It is clear that the assumption that neuronal chemokines are involved in neuron–microglia signaling is no longer based on the finding that damaged neurons rapidly alter chemokine expression patterns and that microglia express the corresponding receptors [63–65]. Studies now show that microglia activation is reduced in mice with genetically disturbed chemokine function, indicating an important role of chemokines in microglia activation. Recent data even suggest that neurosupportive and neurotoxic microglia activity are associated with chemokine receptor expression [125]. The ultimate effects of neuronal chemokines are likely dependent on injury type, brain region, and disruption of the blood–brain barrier [53, 79, 116]. Whereas the exact role of neuronal chemokines in neuron–microglia signaling remains obscure, their importance in regulating damage responses is becoming apparent.

Neuron–Neuron Interaction

Various reports indicate that chemokines influence neuronal development, differentiation [126, 127], survival [128–130], electrophysiological properties [93, 131, 132], and synaptic transmission [26, 92, 133]. Because neurons can express numerous chemokines, autocrine and paracrine contributions of neuronal chemokines are likely.

Neuroprotection

Neuronal cell death, the ultimate consequence of all neuroinflammatory conditions, has been studied extensively in vitro.

However, there are relatively few in vitro models that can be extrapolated to pathological conditions leading to neuronal death in vivo. One of the most prominent models is glutamate or NMDA-induced neurotoxicity, a model for excitotoxicity, which is most likely involved in various neurodegenerative diseases. β-amyloid-induced neuronal death serves as a model that may explain the loss of neurons in Alzheimer's disease, whereas exposure of neuronal cultures to HIV proteins gp120 or HIV_{tat} are aimed to elucidate neuronal death in HIV-dependent neurodegeneration [134–137]. Several reports indicate that neuronal chemokines may protect neurons from these toxic conditions. In vitro, CX3CL1 is known to protect neurons from glutamate-induced toxicity [78, 138], gp120-induced neuronal death [64, 139], and death induced by deprivation of trophic support [140].

Similar to CX3CL1, CCL2 exposure is shown to protect neurons from glutamate- and HIV-tat-induced neurotoxicity [141, 142]. However, CCL2 exposure was not protective in β-amyloid-dependent neuronal death [141]. As exposure of neuronal cells to chemokines is known to activate the putatively neuroprotective MEK/ERK and PI3-K/Akt signaling pathways [78, 138–140], it is reasonable to argue that chemokine-dependent protection is mediated by these pathways. Indeed, inhibition of both pathways completely abolished the neuroprotective effects of CX3CL1 in gp120- and glutamate-induced neurotoxicity in hippocampal neurons [64, 78]. Interestingly, in case of glutamate-dependent neurotoxicity, the involvement of MEK/ERK and PI3-K/Akt signaling pathways was only evident when CX3CL1 was applied together with glutamate [78]. CX3CL1 exposure was shown to be protective even when the chemokine was applied up to 8 h after the glutamate stimulus. However, an inhibition of MEK/ERK and PI3-K/Akt pathways did not affect the protective activity of delayed CX3CL1 exposure, indicating that CX3CL1 may activate additional pathways in neurons that lead to neuroprotection [78]. The effect of CXCL12 on neuronal death is contradictory. Although several reports indicate that CXCL12 exposure may protect neurons from gp120-induced neuronal death, most papers describe a toxic effect of CXCL12 in neuronal cultures (see below) [64, 143].

Neurotoxicity

Approximately 10% of HIV-infected patients develop HIV-1 associated dementia (HAD). It has been shown that the viral protein gp120 itself is neurotoxic [144], indicating that the neuronal loss in HAD is not only due to inflammation occurring after the virus enters the brain but also because of direct toxic effects of viral proteins (see for recent review, [145]). It was shown in 1998 that the neurotoxic effect of gp120 is mediated via the chemokine receptor CXCR4 [146], findings that have been corroborated in subsequent years by various groups [64, 102, 147, 148]. The viral protein gp120 binds and activates CXCR4, the main coreceptor utilized by HIV-1 to infect T cells. CXCR4 has subsequently become the best investigated chemokine receptor with respect to neurotoxicity, and its involvement in neurotoxic signaling has been demonstrated by use of the specific CXCR4 antagonist AMD31000 [102, 147]. The HIV-derived protein gp120 shows agonist activity on CXCR4, and therefore, it is not surprising that its ligand CXCL12 has also been described to be neurotoxic [102, 143, 146, 148, 149]. Currently, there is little information on intracellular signaling pathways that are activated by CXCR4 and subsequently lead to neuronal death. One recent report indicates the involvement of Src activity in CXCL12-induced apoptosis in a neuronal cell line, whereas gp120-induced apoptosis in these cells was independent of Src activity [149]. Interestingly, CXCL12 and gp120 had different effects on ERK activation in neurons and astrocytes [102], indicating that CXCR4 signaling exerts both ligand and cell-type specific effects. The effect of CXCL12 is further complicated by matrix metalloproteinase-2, which was shown to remove the first four amino acids of CXCL12, resulting in a truncated form of CXCL12 [150]. This truncated form was found to be highly neurotoxic compared to the full-length CXCL12, which remarkably was not mediated by CXCR4 but by a yet unknown PTX-sensitive receptor [150]. Because MMP-2 has also been described in HIV-infected patients, it is reasonable to assume that truncated CXCL12 may be a neurotoxic player in HAD [151].

CXCL12 is not the only neuronal chemokine that exerts neurotoxic effects. Neuronal cell lines and primary human neurons respond to high concentrations of CXCL10 with intracellular calcium transients, caspase activity, and apoptosis [54, 152, 153]. The direct involvement of CXCR3 was demonstrated by the use of an antibody that prevents the activation of CXCR3 and subsequently inhibited CXCL10-dependent neurotoxicity [153].

Chemokinergic Effects on Synaptic Transmission

Recent data show that CXCR4 activation by either gp120 or CXCL12 significantly enhanced giant depolarizing potentials (GDP) in rat neonatal hippocampus [154]. These GDPs only occur in the developing hippocampus and are involved in growth and synapse formation. These data may explain why HIV infections have a greater impact in the developing brain than in adults [152] and show that neuronal chemokines may change the electrophysiological properties of neurons, thereby corroborating earlier findings [131, 132, 155, 156].

The electrophysiological properties of neuronal chemokine receptors have predominantly been studied in cultured

primary neurons or neuronal cell lines and brain slice cultures [157]. Remarkably, in cultures of DRG, cerebellar granule or Purkinje neurons, and hippocampal pyramidal cells, chemokines induced changes in the electrophysiological properties of only 10–20% of the neurons [64, 140, 158, 159]. In addition, several effects of chemokines in neurons were not sensitive to PTX, in contrast to hematopoietic cells, suggesting that chemokine receptors in neurons, although generally accepted, are not solely coupled to $G\alpha_i$ proteins [128, 140, 149]. Whether these chemokinergic PTX-insensitive effects are mediated by neuronal G_z-subunits is yet unclear [160]. Cultured cerebellar and DRG neurons respond to various chemokines with intracellular calcium transients [140]. In DRG neurons, exposure to CX3CL1 and CXCL12 also increased their excitability [158]. Although chemokinergic effects of CX3CL1, CXCL12, CCL2, and CXCL10 in neurons have been reported to modulate the frequency of both spontaneous and activity-dependent neuronal firing, a direct effect on the induction of action potentials has not yet been described [159, 161–164]. Similar to the effects on isolated neurons, CX3CL1, CXCL12, and CXCL10 also affected neuronal signaling in brain slice cultures [26, 78, 91–93, 133, 134, 165, 166]. However, the presence of glia cells (astrocytes, microglia, and oligodendrocytes) in these slice cultures makes it difficult to determine whether the electrophysiological effects of chemokines are mediated by chemokine receptors on neurons and/or on glia cells, as glia cells may also induce electrophysiological changes in neurons [26, 133, 156]. Whether the effects of CXCL12 in brain slice cultures are mediated via chemokine receptors on neurons and/or on glia cells may depend on the concentration, as concentrations up to 1 nM caused a direct decrease in peak and discharge frequency of evoked action potentials in neurons and concentrations higher than 10 nM activated an indirect GABA-mediated hyperpolarization of neurons [92].

Future Directions

As discussed here, neuronal chemokines appear to be versatile messengers in CNS cell interaction. However, several important issues need to be addressed in future studies. To begin with, neuronal CX3CR1 expression in vivo remains controversial. Immunohistochemical analysis revealed CX3CR1 positive neurons in mouse brain sections with little changes under pathological conditions [67], whereas neuronal CX3CR1 expression was never described in studies using genetically modified mice in which CX3CR1-expressing cells are also positive for EGFP [116]. Different microscopic techniques and models of neurodegeneration have been explored in these mice, demonstrating only CX3CR1 expression in resting and activated microglia [79, 105, 106, 116]. An explanation may be that neuronal CX3CR1 expression is at such a low level that detection is difficult to achieve with microscopic techniques. This may also be the case for CXCR3 expression in microglia. Although CXCR3 expression has yet not been described in microglia in vivo, functional evidence derived from CXCR3-deficient mice strongly indicates that microglia do express CXCR3 in vivo [53, 115]. Therefore, it seems appropriate that future experiments concerning the expression of chemokine receptors in CNS cells in vivo also include functional analysis.

Another issue that needs to be addressed in more detail regards cellular localization. Neurons are highly polarized cells, as their function is largely dependent on their morphology and contacts with other cells (e.g. synapses with other neurons). Although neuronal signaling molecules, such as neurotransmitters, neuropeptides, and neurotrophins, are generally found at specific sites, most reports describing neuronal chemokine expression did not address this issue. Interestingly, a few recent publications do suggest a localized expression of chemokines comparable to other neuronal signaling molecules. Our group demonstrated that neuronal CCL21 is transported in vesicles, reaching presynaptic terminals in cortical neurons in vitro [46]. In subsequent studies, these vesicles appeared to be of the large-dense core type, in which other neuronal peptides are also found (e.g. neurotrophins; Stanulovic et al., manuscript in preparation). Moreover, it has been described for several neuronal populations in vivo that CCL2 and CXCL12 colocalize with other neurotransmitters and neuropeptides in synaptic regions [37, 62]. Like neuronal chemokine expression, a site-specific expression of chemokine receptors may exist, as is suggested by CXCR4 redistribution in the axonal and dendritic compartment of hippocampal neurons after prolonged CXCL12 exposure [167]. Because a localized expression of chemokines and their receptors may have a consequence for their role in cell interaction, future studies on neuronal chemokine expression may address this issue.

At last, as all reports indicating that chemokine exposure alters the excitability of neurons used exogenous chemokines, it is yet unknown whether chemokines released from neurons have similar effects.

Conclusion

Knowledge on the spatial and temporal expression of neuronal chemokines and their regulation under physiological and pathological conditions is increasing rapidly. As CNS cells can express the corresponding chemokine receptors, contribution of these neuronal chemokines to

CNS cell interaction is conceivable. This assumption is corroborated by various in vitro and in vivo studies. For example, the following effects of neuronal chemokines were observed in vitro: in astrocytes proliferation and migration, in microglia migration and neurotoxic and neuroprotective activity and in neurons electrophysiological changes, neurotoxicity, and neuroprotection. Further, the synaptic transmission between neurons seems to be influenced by the action of neuronal chemokines on neurons and/or glia cells. In vivo studies support the important role of chemokines in migration and neurotoxic and neuroprotective activity of microglia upon CNS injury and neuroinflammation. Further exploration of the roles of neuronal chemokines in CNS cell interaction is needful, as insight into the role of neuronal chemokines in CNS injury and neuroinflammation may contribute to the development of therapeutic strategies.

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References

1. Yoshimura T (1987) Purification of a human monocyte-derived neutrophil chemotactic factor that has peptide sequence similarity to other host defense cytokines. Proc Natl Acad Sci USA 84:9233–9237
2. Laing KJ (2004) Chemokines. Dev Comp Immunol 28:443–460
3. Murphy PM (2002) International Union of Pharmacology. XXX. Update on chemokine receptor nomenclature. Pharmacol Rev 54:227–229
4. Fernandez EJ (2002) Structure, function, and inhibition of chemokines. Annu Rev Pharmacol Toxicol 42:469–499
5. Rossi D (2000) The biology of chemokines and their receptors. Annu Rev Immunol 18:217–242
6. Biber K (2002) Neuronal SLC (CCL21) expression: implications for the neuron–microglial signaling system. Ernst Schering Res Found Workshop 45–60
7. Dijkstra IM (2004) Cutting edge: activity of human adult microglia in response to CC chemokine ligand 21. J Immunol 172:2744–2747
8. Soto H (1998) The CC chemokine 6Ckine binds the CXC chemokine receptor CXCR3. Proc Natl Acad Sci USA 95: 8205–8210
9. Neves SR (2002) G protein pathways. Science 296:1636–1639
10. Murphy PM (1996) Chemokine receptors: structure, function and role in microbial pathogenesis. Cytokine Growth Factor Rev 7:47–64
11. Balkwill F (1998) The molecular and cellular biology of the chemokines. J Viral Hepat 5:1–14
12. Mellado M (2001) Chemokine receptor homo- or heterodimerization activates distinct signaling pathways. EMBO J 20:2497–2507
13. Laudanna C (2006) Right on the spot. Chemokine triggering of integrin-mediated arrest of rolling leukocytes. Thromb Haemost 95:5–11
14. Rittner HL (2006) Chemokines and pain. Curr Opin Investig Drugs 7:643–646
15. Baggiolini M (1998) Chemokines and leukocyte traffic. Nature 392:565–568
16. Moser B (2001) Lymphocyte traffic control by chemokines. Nat Immunol 2:123–128
17. Rot A (2004) Chemokines in innate and adaptive host defense: basic chemokinese grammar for immune cells. Annu Rev Immunol 22:891–928
18. Benelli R (2006) Cytokines and chemokines as regulators of angiogenesis in health and disease. Curr Pharm Des 12:3101–3115
19. Charo IF (2006) The many roles of chemokines and chemokine receptors in inflammation. N Engl J Med 354:610–621
20. Kunkel SL (1999) Through the looking glass: the diverse in vivo activities of chemokines. J Clin Invest 104:1333–1334
21. Mackay CR (2001) Chemokines: immunology's high impact factors. Nat Immunol 2:95–101
22. Murray LA (2006) Role of chemokines in severe asthma. Curr Drug Targets 7:579–588
23. Pease JE (2006) Chemokines and their receptors in allergic disease. J Allergy Clin Immunol 118:305–318
24. Zlotnik A (2006) Involvement of chemokine receptors in organ-specific metastasis. Contrib Microbiol 13:191–199
25. Ubogu EE (2006) The expression and function of chemokines involved in CNS inflammation. Trends Pharmacol Sci 27:48–55
26. Bertollini C (2006) Fractalkine/CX(3)CL1 depresses central synaptic transmission in mouse hippocampal slices. Neuropharmacology 51:816–821
27. Che X (2001) Monocyte chemoattractant protein-1 expressed in neurons and astrocytes during focal ischemia in mice. Brain Res 902:171–177
28. Ivacko J (1997) Hypoxic-ischemic injury induces monocyte chemoattractant protein-1 expression in neonatal rat brain. J Cereb Blood Flow Metab 17:759–770
29. Pang L (2001) Reduction of inflammatory response in the mouse brain with adenoviral-mediated transforming growth factor-ss1 expression. Stroke 32:544–552
30. Flugel A (2001) Neuronal MCP-1 expression in response to remote nerve injury. J Cereb Blood Flow Metab 21:69–76
31. Schreiber RC (2001) Monocyte chemoattractant protein (MCP)-1 is rapidly expressed by sympathetic ganglion neurons following axonal injury. Neuroreport 12:601–606
32. Tanaka T (2004) Enhanced production of monocyte chemoattractant protein-1 in the dorsal root ganglia in a rat model of neuropathic pain: possible involvement in the development of neuropathic pain. Neurosci Res 48:463–469
33. White FA (2005) Excitatory monocyte chemoattractant protein-1 signaling is up-regulated in sensory neurons after chronic compression of the dorsal root ganglion. Proc Natl Acad Sci USA 102: 14092–14097
34. Zhang J (2006) Spatial and temporal relationship between monocyte chemoattractant protein-1 expression and spinal glial activation following peripheral nerve injury. J Neurochem 97:772–783
35. Baron P (2005) Production of monocyte chemoattractant protein-1 in amyotrophic lateral sclerosis. Muscle Nerve 32:541–544
36. Henkel JS (2006) The chemokine MCP-1 and the dendritic and myeloid cells it attracts are increased in the mSOD1 mouse model of ALS. Mol Cell Neurosci 31:427–437
37. Banisadr G (2005) Highly regionalized neuronal expression of monocyte chemoattractant protein-1 (MCP-1/CCL2) in rat brain: evidence for its colocalization with neurotransmitters and neuropeptides. J Comp Neurol 489:275–292
38. Coughlan CM (2000) Expression of multiple functional chemokine receptors and monocyte chemoattractant protein-1 in human neurons. Neuroscience 97:591–600
39. Meng SZ (1999) Developmental expression of monocyte chemoattractant protein-1 in the human cerebellum and brainstem. Brain Dev 21:30–35

40. Xia MQ (1998) Immunohistochemical study of the beta-chemokine receptors CCR3 and CCR5 and their ligands in normal and Alzheimer's disease brains. Am J Pathol 153:31–37
41. Bakhiet M (2001) RANTES promotes growth and survival of human first-trimester forebrain astrocytes. Nat Cell Biol 3:150–157
42. Schluter D (2001) Toxoplasma gondii infection of neurons induces neuronal cytokine and chemokine production, but gamma interferon- and tumor necrosis factor-stimulated neurons fail to inhibit the invasion and growth of *T. gondii*. Infect Immun 69:7889–7893
43. Klein RS (2005) Neuronal CXCL10 directs CD8+ T-cell recruitment and control of West Nile virus encephalitis. J Virol 79:11457–11466
44. Patterson CE (2003) Measles virus infection induces chemokine synthesis by neurons. J Immunol 171:3102–3109
45. Biber K (2001) Ischemia-induced neuronal expression of the microglia attracting chemokine Secondary Lymphoid-tissue Chemokine (SLC). Glia 34:121–133
46. de Jong EK (2005) Vesicle-mediated transport and release of CCL21 in endangered neurons: a possible explanation for microglia activation remote from a primary lesion. J Neurosci 25:7548–7557
47. Muller G (2003) Concerted action of the chemokine and lymphotoxin system in secondary lymphoid-organ development. Curr Opin Immunol 15:217–224
48. Aloisi F (2006) Lymphoid neogenesis in chronic inflammatory diseases. Nat Rev Immunol 6:205–217
49. Chen SC (2002) Central nervous system inflammation and neurological disease in transgenic mice expressing the CC chemokine CCL21 in oligodendrocytes. J Immunol 168:1009–1017
50. Chen SC (2002) Ectopic expression of the murine chemokines CCL21a and CCL21b induces the formation of lymph node-like structures in pancreas, but not skin, of transgenic mice. J Immunol 168:1001–1008
51. Yabe T (2004) Treatment of cerebellar granule cell neurons with the neurotrophic factor pigment epithelium-derived factor in vitro enhances expression of other neurotrophic factors as well as cytokines and chemokines. J Neurosci Res 77:642–652
52. Wang X (1998) Prolonged expression of interferon-inducible protein-10 in ischemic cortex after permanent occlusion of the middle cerebral artery in rat. J Neurochem 71:1194–1204
53. Rappert A (2004) CXCR3-dependent microglial recruitment is essential for dendrite loss after brain lesion. J Neurosci 24:8500–8509
54. Sui Y (2004) Neuronal apoptosis is mediated by CXCL10 overexpression in simian human immunodeficiency virus encephalitis. Am J Pathol 164:1557–1566
55. Gleichmann M (2000) Cloning and characterization of SDF-1gamma, a novel SDF-1 chemokine transcript with developmentally regulated expression in the nervous system. Eur J Neurosci 12:1857–1866
56. Stumm RK (2002) A dual role for the SDF-1/CXCR4 chemokine receptor system in adult brain: isoform-selective regulation of SDF-1 expression modulates CXCR4-dependent neuronal plasticity and cerebral leukocyte recruitment after focal ischemia. J Neurosci 22:5865–5878
57. Bajetto A (1999) Glial and neuronal cells express functional chemokine receptor CXCR4 and its natural ligand stromal cell-derived factor 1. J Neurochem 73:2348–2357
58. Ohtani Y (1998) Expression of stromal cell-derived factor-1 and CXCR4 chemokine receptor mRNAs in cultured rat glial and neuronal cells. Neurosci Lett 249:163–166
59. Rostasy K (2003) SDF-1alpha is expressed in astrocytes and neurons in the AIDS dementia complex: an in vivo and in vitro study. J Neuropathol Exp Neurol 62:617–626
60. Tham TN (2001) Developmental pattern of expression of the alpha chemokine stromal cell-derived factor 1 in the rat central nervous system. Eur J Neurosci 13:845–856
61. Banisadr G (2003) Highly regionalized distribution of stromal cell-derived factor-1/CXCL12 in adult rat brain: constitutive expression in cholinergic, dopaminergic and vasopressinergic neurons. Eur J Neurosci 18:1593–1606
62. Callewaere C (2006) The chemokine SDF-1/CXCL12 modulates the firing pattern of vasopressin neurons and counteracts induced vasopressin release through CXCR4. Proc Natl Acad Sci USA 103:8221–8226
63. Harrison JK (1998) Role for neuronally derived fractalkine in mediating interactions between neurons and CX3CR1-expressing microglia. Proc Natl Acad Sci U S A 95:10896–10901
64. Meucci O (1998) Chemokines regulate hippocampal neuronal signaling and gp120 neurotoxicity. Proc Natl Acad Sci USA 95:14500–14505
65. Nishiyori A (1998) Localization of fractalkine and CX3CR1 mRNAs in rat brain: does fractalkine play a role in signaling from neuron to microglia? FEBS Lett 429:167–172
66. Schwaeble WJ (1998) Neuronal expression of fractalkine in the presence and absence of inflammation. FEBS Lett 439:203–207
67. Hughes PM (2002) Expression of fractalkine (CX3CL1) and its receptor, CX3CR1, during acute and chronic inflammation in the rodent CNS. Glia 37:314–327
68. Sunnemark D (2005) CX3CL1 (fractalkine) and CX3CR1 expression in myelin oligodendrocyte glycoprotein-induced experimental autoimmune encephalomyelitis: kinetics and cellular origin. J Neuroinflammation 2:17
69. Tarozzo G (2003) Fractalkine protein localization and gene expression in mouse brain. J Neurosci Res 73:81–88
70. Pan Y (1997) Neurotactin, a membrane-anchored chemokine upregulated in brain inflammation. Nature 387:611–617
71. Garton KJ (2001) Tumor necrosis factor-alpha-converting enzyme (ADAM17) mediates the cleavage and shedding of fractalkine (CX3CL1). J Biol Chem 276:37993–38001
72. Hundhausen C (2003) The disintegrin-like metalloproteinase ADAM10 is involved in constitutive cleavage of CX3CL1 (fractalkine) and regulates CX3CL1-mediated cell–cell adhesion. Blood 102:1186–1195
73. Chapman GA (2000) Fractalkine cleavage from neuronal membranes represents an acute event in the inflammatory response to excitotoxic brain damage. J Neurosci 20:RC87
74. Erichsen D (2003) Neuronal injury regulates fractalkine: relevance for HIV-1 associated dementia. J Neuroimmunol 138:144–155
75. Hatori K (2002) Fractalkine and fractalkine receptors in human neurons and glial cells. J Neurosci Res 69:418–426
76. Maciejewski-Lenoir D (1999) Characterization of fractalkine in rat brain cells: migratory and activation signals for CX3CR-1-expressing microglia. J Immunol 163:1628–1635
77. Mizuno T (2003) Production and neuroprotective functions of fractalkine in the central nervous system. Brain Res 979:65–70
78. Limatola C (2005) Chemokine CX3CL1 protects rat hippocampal neurons against glutamate-mediated excitotoxicity. J Neuroimmunol 166:19–28
79. Cardona AE (2006) Control of microglial neurotoxicity by the fractalkine receptor. Nat Neurosci 9:917–924
80. Volterra A (2005) Astrocytes, from brain glue to communication elements: the revolution continues. Nat Rev Neurosci 6:626–640
81. Dorf ME (2000) Astrocytes express functional chemokine receptors. J Neuroimmunol 111:109–121
82. Ambrosini E (2004) Chemokines and glial cells: a complex network in the central nervous system. Neurochem Res 29:1017–1038
83. Andjelkovic AV (2002) Functional expression of CCR2 by human fetal astrocytes. J Neurosci Res 70:219–231
84. Biber K (2002) Functional expression of CXCR3 in cultured mouse and human astrocytes and microglia. Neuroscience 112:487–497

85. Klein RS (1999) Chemokine receptor expression and signaling in macaque and human fetal neurons and astrocytes: implications for the neuropathogenesis of AIDS. J Immunol 163:1636–1646
86. Tanabe S (1997) Functional expression of the CXC-chemokine receptor-4/fusin on mouse microglial cells and astrocytes. J Immunol 159:905–911
87. Bajetto A (2001) Stromal cell-derived factor-1alpha induces astrocyte proliferation through the activation of extracellular signal-regulated kinases 1/2 pathway. J Neurochem 77:1226–1236
88. Boddeke EW (1999) Cultured rat microglia express functional beta-chemokine receptors. J Neuroimmunol 98:176–184
89. Kettenmann H (1995) Neuroglia, 2nd edn. Oxford University Press, New York, pp 229–239
90. Bezzi P (2001) CXCR4-activated astrocyte glutamate release via TNFalpha: amplification by microglia triggers neurotoxicity. Nat Neurosci 4:702–710
91. Guyon A (2005) Complex effects of stromal cell-derived factor-1 alpha on melanin-concentrating hormone neuron excitability. Eur J Neurosci 21:701–710
92. Guyon A (2006) Stromal cell-derived factor-1alpha modulation of the excitability of rat substantia nigra dopaminergic neurones: presynaptic mechanisms. J Neurochem 96:1540–1550
93. Ragozzino D (2002) Stimulation of chemokine CXC receptor 4 induces synaptic depression of evoked parallel fibers inputs onto Purkinje neurons in mouse cerebellum. J Neuroimmunol 127:30–36
94. Eng LF (1994) GFAP and astrogliosis. Brain Pathol 4:229–237
95. Goldberg SH (2001) CXCR3 expression in human central nervous system diseases. Neuropathol Appl Neurobiol 27:127–138
96. Simpson J (2000) Expression of the beta-chemokine receptors CCR2, CCR3 and CCR5 in multiple sclerosis central nervous system tissue. J Neuroimmunol 108:192–200
97. Tanuma N (2006) Chemokine expression by astrocytes plays a role in microglia/macrophage activation and subsequent neurodegeneration in secondary progressive multiple sclerosis. Acta Neuropathol (Berl) 112:195–204
98. Flynn G (2003) Regulation of chemokine receptor expression in human microglia and astrocytes. J Neuroimmunol 136:84–93
99. Rezaie P (2002) Expression of beta-chemokines and chemokine receptors in human fetal astrocyte and microglial co-cultures: potential role of chemokines in the developing CNS. Glia 37:64–75
100. Han Y (2001) TNF-alpha mediates SDF-1 alpha-induced NF-kappa B activation and cytotoxic effects in primary astrocytes. J Clin Invest 108:425–435
101. Han Y (2001) TNF-alpha down-regulates CXCR4 expression in primary murine astrocytes. Brain Res 888:1–10
102. Lazarini F (2000) Differential signalling of the chemokine receptor CXCR4 by stromal cell-derived factor 1 and the HIV glycoprotein in rat neurons and astrocytes. Eur J Neurosci 12:117–125
103. Heesen M (1996) Mouse astrocytes respond to the chemokines MCP-1 and KC, but reverse transcriptase-polymerase chain reaction does not detect mRNA for the KC or new MCP-1 receptor. J Neurosci Res 45:382–391
104. Odemis V (2002) Interleukin-6 and cAMP induce stromal cell-derived factor-1 chemotaxis in astroglia by up-regulating CXCR4 cell surface expression. Implications for brain inflammation. J Biol Chem 277:39801–39808
105. Davalos D (2005) ATP mediates rapid microglial response to local brain injury in vivo. Nat Neurosci 8:752–758
106. Nimmerjahn A (2005) Resting microglial cells are highly dynamic surveillants of brain parenchyma in vivo. Science 308:1314–1318
107. Town T (2005) The microglial "activation" continuum: from innate to adaptive responses. J Neuroinflammation 2:24
108. Kim SU (2005) Microglia in health and disease. J Neurosci Res 81:302–313
109. Kreutzberg GW (1996) Microglia: a sensor for pathological events in the CNS. Trends Neurosci 19:312–318
110. Raivich G (1999) Neuroglial activation repertoire in the injured brain: graded response, molecular mechanisms and cues to physiological function. Brain Res Brain Res Rev 30:77–105
111. Streit WJ (1999) Reactive microgliosis. Prog Neurobiol 57:563–581
112. Cross AK (1999) Chemokines induce migration and changes in actin polymerization in adult rat brain microglia and a human fetal microglial cell line in vitro. J Neurosci Res 55:17–23
113. Hulshof S (2003) CX3CL1 and CX3CR1 expression in human brain tissue: noninflammatory control versus multiple sclerosis. J Neuropathol Exp Neurol 62:899–907
114. Kuipers HF (2006) Simvastatin affects cell motility and actin cytoskeleton distribution of microglia. Glia 53:115–123
115. Rappert A (2002) Secondary lymphoid tissue chemokine (CCL21) activates CXCR3 to trigger a Cl-current and chemotaxis in murine microglia. J Immunol 168:3221–3226
116. Jung S (2000) Analysis of fractalkine receptor CX(3)CR1 function by targeted deletion and green fluorescent protein reporter gene insertion. Mol Cell Biol 20:4106–4114
117. Soriano SG (2002) Mice deficient in fractalkine are less susceptible to cerebral ischemia–reperfusion injury. J Neuroimmunol 125:59–65
118. Zujovic V (2000) Fractalkine modulates TNF-alpha secretion and neurotoxicity induced by microglial activation. Glia 29:305–315
119. Boehme SA (2000) The chemokine fractalkine inhibits Fas-mediated cell death of brain microglia. J Immunol 165:397–403
120. Bechmann I (2000) Involvement of non-neuronal cells in entorhinal-hippocampal reorganization following lesions. Ann N Y Acad Sci 911:192–206
121. Banati RB (2002) Brain plasticity and microglia: is transsynaptic glial activation in the thalamus after limb denervation linked to cortical plasticity and central sensitisation? J Physiol Paris 96:289–299
122. Gerard C (2001) Chemokines: back to the future? Nat Cell Biol 3:E53–E54
123. Muessel MJ (2002) Ablation of the chemokine monocyte chemoattractant protein-1 delays retrograde neuronal degeneration, attenuates microglial activation, and alters expression of cell death molecules. Brain Res Mol Brain Res 103:12–27
124. Muessel MJ (2000) Early and specific expression of monocyte chemoattractant protein-1 in the thalamus induced by cortical injury. Brain Res 870:211–221
125. Li H (2006) Different neurotropic pathogens elicit neurotoxic CCR9- or neurosupportive CXCR3-expressing microglia. J Immunol 177:3644–3656
126. Lieberam I (2005) A Cxcl12–CXCR4 chemokine signaling pathway defines the initial trajectory of mammalian motor axons. Neuron 47:667–679
127. Pujol F (2005) The chemokine SDF-1 differentially regulates axonal elongation and branching in hippocampal neurons. J Cell Sci 118:1071–1080
128. Limatola C (2000) The chemokine growth-related gene product beta protects rat cerebellar granule cells from apoptotic cell death through alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionate receptors. Proc Natl Acad Sci U S A 97:6197–6201
129. Luo Q (2005) *N*-methyl-D-aspartate attenuates CXCR2-mediated neuroprotection through enhancing the receptor phosphorylation and blocking the receptor recycling. Mol Pharmacol 68:528–537
130. Watson K (2005) Macrophage inflammatory protein 2 inhibits beta-amyloid peptide (1-42)-mediated hippocampal neuronal apoptosis through activation of mitogen-activated protein kinase and phosphatidylinositol 3-kinase signaling pathways. Mol Pharmacol 67:757–765
131. Giovannelli A (1998) CXC chemokines interleukin-8 (IL-8) and growth-related gene product alpha (GROalpha) modulate Pur-

kinje neuron activity in mouse cerebellum. J Neuroimmunol 92:122–132
132. Puma C (2001) The chemokine interleukin-8 acutely reduces Ca(2+) currents in identified cholinergic septal neurons expressing CXCR1 and CXCR2 receptor mRNAs. J Neurochem 78:960–971
133. Limatola C (2000) SDF-1alpha-mediated modulation of synaptic transmission in rat cerebellum. Eur J Neurosci 12:2497–2504
134. Dong J (2006) Human immunodeficiency virus type 1 gp120 inhibits long-term potentiation via chemokine receptor CXCR4 in rat hippocampal slices. J Neurosci Res 83:489–496
135. Kaul M (2001) Pathways to neuronal injury and apoptosis in HIV-associated dementia. Nature 410:988–994
136. Masliah E (1992) Selective neuronal vulnerability in HIV encephalitis. J Neuropathol Exp Neurol 51:585–593
137. Masliah E (1997) Role of amyloid precursor protein in the mechanisms of neurodegeneration in Alzheimer's disease. Lab Invest 77:197–209
138. Deiva K (2004) Fractalkine reduces *N*-methyl-*d*-aspartate-induced calcium flux and apoptosis in human neurons through extracellular signal-regulated kinase activation. Eur J Neurosci 20:3222–3232
139. Meucci O (2000) Expression of CX3CR1 chemokine receptors on neurons and their role in neuronal survival. Proc Natl Acad Sci U S A 97:8075–8080
140. Gillard SE (2002) Expression of functional chemokine receptors by rat cerebellar neurons. J Neuroimmunol 124:16–28
141. Bruno V (2000) Neuroprotective activity of chemokines against *N*-methyl-D-aspartate or beta-amyloid-induced toxicity in culture. Eur J Pharmacol 399:117–121
142. Eugenin EA (2003) MCP-1 (CCL2) protects human neurons and astrocytes from NMDA or HIV-tat-induced apoptosis. J Neurochem 85:1299–1311
143. Catani MV (2000) gp120 induces cell death in human neuroblastoma cells through the CXCR4 and CCR5 chemokine receptors. J Neurochem 74:2373–2379
144. Brenneman DE (1988) Neuronal cell killing by the envelope protein of HIV and its prevention by vasoactive intestinal peptide. Nature 335:639–642
145. Kaul M (2007) HIV-1 coreceptors CCR5 and CXCR4 both mediate neuronal cell death but CCR5 paradoxically can also contribute to protection. Cell Death Differ (in press)
146. Hesselgesser J (1998) Neuronal apoptosis induced by HIV-1 gp120 and the chemokine SDF-1 alpha is mediated by the chemokine receptor CXCR4. Curr Biol 8:595–598
147. Bachis A (2004) The chemokine receptor CXCR4 and not the *N*-methyl-D-aspartate receptor mediates gp120 neurotoxicity in cerebellar granule cells. J Neurosci Res 75:75–82
148. Kaul M (1999) Chemokines and activated macrophages in HIV gp120-induced neuronal apoptosis. Proc Natl Acad Sci USA 96:8212–8216
149. Geeraerts T (2006) Effects of SDF-1alpha and gp120IIIB on apoptotic pathways in SK-N-SH neuroblastoma cells. Neurosci Lett 399:115–120
150. Zhang K (2003) HIV-induced metalloproteinase processing of the chemokine stromal cell derived factor-1 causes neurodegeneration. Nat Neurosci 6:1064–1071
151. Ransohoff RM (2003) Snip–snip, kill–kill: truncated SDF-1 and HIV-associated neurodegeneration. Nat Neurosci 6:1009–1011
152. Sui Y (2006) CXCL10-induced cell death in neurons: role of calcium dysregulation. Eur J Neurosci 23:957–964
153. van Marle G (2004) Human immunodeficiency virus type 1 Nef protein mediates neural cell death: a neurotoxic role for IP-10. Virology 329:302–318
154. Kasyanov A (2006) HIV-1 gp120 enhances giant depolarizing potentials via chemokine receptor CXCR4 in neonatal rat hippocampus. Eur J Neurosci 23:1120–1128
155. Cho C (2002) Chemokine receptors and neural function. J Neurovirol 8:573–584
156. Ragozzino D (1998) Modulation of the neurotransmitter release in rat cerebellar neurons by GRO beta. Neuroreport 9:3601–3606
157. Oh SB (2003) Electrophysiological analysis of neuronal chemokine receptors. Methods 29:335–344
158. Oh SB (2001) Chemokines and glycoprotein120 produce pain hypersensitivity by directly exciting primary nociceptive neurons. J Neurosci 21:5027–5035
159. Oh SB (2002) Regulation of calcium currents by chemokines and their receptors. J Neuroimmunol 123:66–75
160. Tran PB (2003) Chemokine receptors in the brain: a developing story. J Comp Neurol 457:1–6
161. Gosselin RD (2005) Constitutive expression of CCR2 chemokine receptor and inhibition by MCP-1/CCL2 of GABA-induced currents in spinal cord neurones. J Neurochem 95:1023–1034
162. Guyon A (2005) Stromal cell-derived factor-1alpha directly modulates voltage-dependent currents of the action potential in mammalian neuronal cells. J Neurochem 93:963–973
163. Nelson TE (2004) The chemokine CXCL10 modulates excitatory activity and intracellular calcium signaling in cultured hippocampal neurons. J Neuroimmunol 156:74–87
164. van Gassen KL (2005) The chemokine CCL2 modulates Ca2+ dynamics and electrophysiological properties of cultured cerebellar Purkinje neurons. Eur J Neurosci 21:2949–2957
165. Liu Z (2003) Frequency modulation of synchronized Ca2+ spikes in cultured hippocampal networks through G-protein-coupled receptors. J Neurosci 23:4156–4163
166. Vlkolinsky R (2004) Acute exposure to CXC chemokine ligand 10, but not its chronic astroglial production, alters synaptic plasticity in mouse hippocampal slices. J Neuroimmunol 150:37–47
167. Baudouin SJ (2006) Dendrite-selective redistribution of the chemokine receptor CXCR4 following agonist stimulation. Mol Cell Neurosci 33(2):160–169
168. Jo N (2003) Upregulation of chemokine expression in the retinal vasculature in ischemia–reperfusion injury. Invest Ophthalmol Vis Sci 44:4054–4060
169. Puri V (2006) Effects of oestrogen on trigeminal ganglia in culture: implications for hormonal effects on migraine. Cephalalgia 26:33–42
170. Tong N (2000) Neuronal fractalkine expression in HIV-1 encephalitis: roles for macrophage recruitment and neuroprotection in the central nervous system. J Immunol 164:1333–1339
171. Lindia JA (2005) Induction of CX3CL1 expression in astrocytes and CX3CR1 in microglia in the spinal cord of a rat model of neuropathic pain. J Pain 6:434–438
172. Verge GM (2004) Fractalkine (CX3CL1) and fractalkine receptor (CX3CR1) distribution in spinal cord and dorsal root ganglia under basal and neuropathic pain conditions. Eur J Neurosci 20:1150–1160
173. McManus CM (2000) Chemokine and chemokine-receptor expression in human glial elements: induction by the HIV protein, Tat, and chemokine autoregulation. Am J Pathol 156:1441–1453
174. Andjelkovic AV (1999) Expression of binding sites for beta chemokines on human astrocytes. Glia 28:225–235
175. Croitoru-Lamoury J (2003) Expression of chemokines and their receptors in human and simian astrocytes: evidence for a central role of TNF alpha and IFN gamma in CXCR4 and CCR5 modulation. Glia 41:354–370
176. Mahajan SD (2005) Morphine modulates chemokine gene regulation in normal human astrocytes. Clin Immunol 115:323–332
177. Banisadr G (2002) Distribution, cellular localization and functional role of CCR2 chemokine receptors in adult rat brain. J Neurochem 81:257–269
178. Jee Y (2002) Upregulation of monocyte chemotactic protein-1 and CC chemokine receptor 2 in the central nervous system is

closely associated with relapse of autoimmune encephalomyelitis in Lewis rats. J Neuroimmunol 128:49–57
179. van der Meer P (2001) Expression pattern of CXCR3, CXCR4, and CCR3 chemokine receptors in the developing human brain. J Neuropathol Exp Neurol 60:25–32
180. Eugenin EA (2005) HIV-1 tat protein induces a migratory phenotype in human fetal microglia by a CCL2 (MCP-1)-dependent mechanism: possible role in NeuroAIDS. Glia 49:501–510
181. Galasso JM (2000) Acute excitotoxic injury induces expression of monocyte chemoattractant protein-1 and its receptor, CCR2, in neonatal rat brain. Exp Neurol 165:295–305
182. Galasso JM (2000) Experimental gliosarcoma induces chemokine receptor expression in rat brain. Exp Neurol 161:85–95
183. Abbadie C (2003) Impaired neuropathic pain responses in mice lacking the chemokine receptor CCR2. Proc Natl Acad Sci USA 100:7947–7952
184. van der Meer P (2000) Immunohistochemical analysis of CCR2, CCR3, CCR5, and CXCR4 in the human brain: potential mechanisms for HIV dementia. Exp Mol Pathol 69:192–201
185. Banisadr G (2005) Constitutive neuronal expression of CCR2 chemokine receptor and its colocalization with neurotransmitters in normal rat brain: functional effect of MCP-1/CCL2 on calcium mobilization in primary cultured neurons. J Comp Neurol 492:178–192
186. Simpson JE (2000) Expression of the interferon-gamma-inducible chemokines IP-10 and Mig and their receptor, CXCR3, in multiple sclerosis lesions. Neuropathol Appl Neurobiol 26:133–142
187. Kremlev SG (2005) Interleukin-10 inhibits endotoxin-induced pro-inflammatory cytokines in microglial cell cultures. J Neuroimmunol 162:71–80
188. Kremlev SG (2004) Differential expression of chemokines and chemokine receptors during microglial activation and inhibition. J Neuroimmunol 149:1–9
189. Xia MQ (2000) Expression of the chemokine receptor CXCR3 on neurons and the elevated expression of its ligand IP-10 in reactive astrocytes: in vitro ERK1/2 activation and role in Alzheimer's disease. J Neuroimmunol 108:227–235
190. Lavi E (1997) CXCR-4 (Fusin), a co-receptor for the type 1 human immunodeficiency virus (HIV-1), is expressed in the human brain in a variety of cell types, including microglia and neurons. Am J Pathol 151:1035–1042
191. Sanders VJ (1998) Chemokines and receptors in HIV encephalitis. AIDS 12:1021–1026
192. Boutet A (2001) Isolated human astrocytes are not susceptible to infection by M- and T-tropic HIV-1 strains despite functional expression of the chemokine receptors CCR5 and CXCR4. Glia 34:165–177
193. Guillemin GJ (2003) Quinolinic acid upregulates chemokine production and chemokine receptor expression in astrocytes. Glia 41:371–381
194. Okamoto M (2005) HIV-1-infected macrophages induce astrogliosis by SDF-1alpha and matrix metalloproteinases. Biochem Biophys Res Commun 336:1214–1220
195. Sabri F (1999) Nonproductive human immunodeficiency virus type 1 infection of human fetal astrocytes: independence from CD4 and major chemokine receptors. Virology 264:370–384
196. Zheng J (1999) Intracellular CXCR4 signaling, neuronal apoptosis and neuropathogenic mechanisms of HIV-1-associated dementia. J Neuroimmunol 98:185–200
197. Banisadr G (2002) Neuroanatomical distribution of CXCR4 in adult rat brain and its localization in cholinergic and dopaminergic neurons. Eur J Neurosci 16:1661–1671
198. Jiang Y (1998) Chemokine receptor expression in cultured glia and rat experimental allergic encephalomyelitis. J Neuroimmunol 86:1–12
199. Heesen M (1997) Alternate splicing of mouse fusin/CXC chemokine receptor-4: stromal cell-derived factor-1alpha is a ligand for both CXC chemokine receptor-4 isoforms. J Immunol 158:3561–3564
200. Luo Y (2002) RANTES stimulates inflammatory cascades and receptor modulation in murine astrocytes. Glia 39:19–30
201. An SF (2001) Expression of CCR-5/CXCR-4 in spinal cord of patients with AIDS. Acta Neuropathol (Berl) 102:175–180
202. Vallat AV (1998) Localization of HIV-1 co-receptors CCR5 and CXCR4 in the brain of children with AIDS. Am J Pathol 152:167–178
203. Albright AV (1999) Microglia express CCR5, CXCR4, and CCR3, but of these, CCR5 is the principal coreceptor for human immunodeficiency virus type 1 dementia isolates. J Virol 73:205–213
204. Boutet A (2001) Cellular expression of functional chemokine receptor CCR5 and CXCR4 in human embryonic neurons. Neurosci Lett 311:105–108
205. Lecointe D (2002) Human cytomegalovirus infection reduces surface CCR5 expression in human microglial cells, astrocytes and monocyte-derived macrophages. Microbes Infect 4:1401–1408
206. Kanmogne GD (2002) Infection of baboon microglia with SIV–HIV recombinant viruses: role of CD4 and chemokine receptors. AIDS Res Hum Retroviruses 18:557–565
207. Chen S (2005) Transforming growth factor-beta1 increases CXCR4 expression, stromal-derived factor-1alpha-stimulated signalling and human immunodeficiency virus-1 entry in human monocyte-derived macrophages. Immunology 114:565–574
208. Petito CK (2001) Hippocampal injury and alterations in neuronal chemokine co-receptor expression in patients with AIDS. J Neuropathol Exp Neurol 60:377–385
209. Hesselgesser J (1997) CD4-independent association between HIV-1 gp120 and CXCR4: functional chemokine receptors are expressed in human neurons. Curr Biol 7:112–121
210. Westmoreland SV (2002) Developmental expression patterns of CCR5 and CXCR4 in the rhesus macaque brain. J Neuroimmunol 122:146–158
211. Zhang L (1998) In vivo distribution of the human immunodeficiency virus/simian immunodeficiency virus coreceptors: CXCR4, CCR3, and CCR5. J Virol 72:5035–5045
212. Chen S (2002) TGF-beta1 upregulates CX3CR1 expression and inhibits fractalkine-stimulated signaling in rat microglia. J Neuroimmunol 133:46–55
213. Tarozzo G (2002) Expression of fractalkine and its receptor, CX3CR1, in response to ischaemia–reperfusion brain injury in the rat. Eur J Neurosci 15:1663–1668
214. Boddeke EW (1999) Functional expression of the fractalkine (CX3C) receptor and its regulation by lipopolysaccharide in rat microglia. Eur J Pharmacol 374:309–313