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REVIEW

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Chemokines: Key Molecules that Orchestrate Communication among Neurons, Microglia and Astrocytes to Preserve Brain Function

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Abstract—In the CNS, chemokines and chemokine receptors are involved in pleiotropic physiological and pathological activities. Several evidences demonstrated that chemokine signaling in the CNS plays key homeostatic roles and, being expressed on neurons, glia and endothelial cells, chemokines mediate the bidirectional cross-talk among parenchymal cells. An efficient communication between neurons and glia is crucial to establish and maintain a healthy brain environment which ensures normal functionality. Glial cells behave as active sensors of environmental changes induced by neuronal activity or detrimental insults, supporting and exerting neuroprotective activities. In this review we summarize the evidence that chemokines (CXCL12, CX3CL1, CXCL16 and CCL2) modulate neuroprotective processes upon different noxious stimuli and participate to orchestrate neurons-microglia-astrocytes action to preserve and limit brain damage. ***This article is part of a Special Issue entitled: Honoring Ricardo Miledi - outstanding neuroscientist of XX-XXI centuries.***

Key words: chemokines, neuron–glia communication, neuroprotection.

INTRODUCTION

About twenty years ago chemokines (chemotactic cytokines) and their receptors (G-protein coupled receptors) were described in the central nervous system (CNS) in the context of inflammatory diseases, such as Multiple Sclerosis (MS) and Acquired Immuno-Deficiency Syndrome (AIDS) associated dementia, but also in normal brain (Hesselgesser and Horuk, 1999). While the expression of chemokines associated with neuropathological events led researchers to investigate their role in mediating neuroinflammatory and apoptotic events, the expression of these molecules in developing and adult brain suggested homeostatic, physiological roles (Xia and Hyman, 1999; Bajetto et al., 2001; Cartier et al., 2005). At that time, one study already demonstrated that the stromal-cell derived factor-1 SDF-1 (CXCL12), fractalkine (CX3CL1), and regulated upon activation, normal T cell expressed and secreted RANTES (CCL5) counteracted the apoptosis induced by Human Immunodeficiency Virus type I (HIV-1) envelope protein gp120 in cultured hippocampal neurons (Meucci et al., 1998). Moreover Limatola et al. (2000) reported that growth-regulated oncogene beta Groβ (CXCL2) reduced the apoptotic cell death in cerebellar granule cells. These data suggested that chemokines might drive neuroprotection. Since then, the discovery that several chemokines and chemokine receptors are expressed by neurons, microglia, astrocytes and oligodendrocytes suggested they might have a modulatory role in cell to cell communication in the brain (Adler et al., 2006; Biber et al., 2007; Ludwig and Mentlein, 2008; Réaux-Le Goazigo et al., 2013)

Glia-neurons cross-talk sustains brain functions

Despite the neuron-centric view of the brain dominated over the last century, it is now clear that the interplay between neurons and cells within the brain parenchyma (mainly microglia and astrocytes) is determinant for brain functioning, to maintain homeostasis and/or to counteract pathological events in the CNS. Among the glial cells interacting with neurons, microglia (5–12% of brain cells) are highly ramified cells that through the high motility of their branches constantly monitor the brain to sense local alterations (Nimmerjahn et al., 2005). Usually defined as cells of the "innate-immunity" that protect the CNS from pathogens, microglia senses signals of danger, such as PAMPs (pathogen-associated molecular patterns molecules) and DAMPs (damaged-associated molecular patterns molecules) and react to modulate an inflammatory response. Despite their myeloid origin, highly differentiated microglia interact with neurons to regulate homeostatic plasticity (Masgrau et al., 2017). In recent years, it became evident that the so called "resting" microglia are fully active cells that participate to brain functions controlling pruning, elimination and maturation of synapses (Paolicelli et al., 2011; Schafer et al., 2012). Microglial cells play a role during

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development promoting programmed cell death and removing apoptotic neurons and glia (Marín-Teva et al., 2004; Wakselman et al., 2008). In adult brain, microglia contribute to neurogenesis promoting neural precursor proliferation, neuroblast migration, and neuronal differentiation via the secretion of trophic factors (Choi et al., 2008; Yan et al., 2009; Ribeiro Xavier et al., 2015). Astrocytes are specialized cells, organized in non-overlapping domains within the CNS parenchyma and coupled into multicellular networks via gap junctions (Sofroniew and Vinters, 2010). Astrocytes are essential for brain homeostasis affecting: i) the blood–brain-barrier (BBB) integrity; ii) the cerebral blood flow, fluid, ion, pH and transmitter homeostasis; iii) the synaptic function, being components of the (tripartite) synapsis and releasing gliotransmitters; iv) the CNS metabolism regulating energy supply to neurons (Sofroniew and Vinters, 2010). Upon acute brain insults or chronic brain diseases (such as neurodegenerative disease, brain tumor, epilepsy) astrocytes become reactive and undergo morphological, transcriptional and functional changes that can be either beneficial or detrimental (Sofroniew and Vinters, 2010; Liddelow and Barres, 2017). Recently, gene profile analysis of reactive astrocytes revealed at least two subtypes of reactive astrocytes, named A1 and A2 (in analogy to M1-M2 microglia/macrophages definition), depending on the nature of the inducing stimuli (LPS or middle cerebral artery occlusion MCAO) (Zamanian et al., 2012).

A1 astrocytes lose the ability to promote synapses formation, are defective in phagocytosis, and release soluble factors that induce apoptosis of neurons and oligodendrocytes (Zamanian et al., 2012; Liddelow et al., 2017). A2 reactive astrocytes might have protective/reparative functions, since they upregulate neurotrophic factors and thrombospondins (which promote synapses repair) (Liddelow and Barres, 2017). These and other evidence support the notion that the interplay among neurons, microglia and astrocytes orchestrates the endogenous response to limit brain damage upon toxic insult.

Chemokines in healthy brain

Chemokines are small pro-inflammatory cytokines with chemoattractant and regulatory activities (Baggiolini, 1998). Chemokines are important regulators of both the peripheral and central immune response, which largely explains how they contribute to controlling inflammatory processes in the brain.

Indeed, in pathological processes, chemokines represent important neuro-inflammatory mediators that drive leukocytes trafficking and activation into the CNS, facilitating the immune responses, targeting cells of the innate and adaptive immune system (Williams et al., 2014). However, chemokine expression in the CNS is not only related to pathological conditions. Constitutive brain expression of chemokines and their receptors on endothelial cells, neurons and glia, suggests a role for such molecules in mediating homeostatic cross-talk between cells of the brain parenchyma (Williams et al., 2014). The cross-talk among neurons and glia is determinant to establish and maintain a normal brain function. During brain development, chemokines represent signaling molecules that drive the correct migration and axonal pathfinding of neuronal progenitor cells (Tran and Miller, 2003): in particular, CXCL12/CXCR4 pair modulates cerebral cortex (Bagri et al., 2002; Lu et al., 2002; Stumm et al., 2003; Stumm and Höllt, 2007) and cerebellar (Ma et al., 1998; Zou et al., 1998) development. In adult brain, high expression of CXCR4 has been reported in neuronal progenitor cells in the subventricular region and in the subgranular zone of the hippocampus, the two major niches of neuronal stem cells in the adult brain (Stumm et al., 2002; Berger et al., 2007). The expression of CXCL12 in the hippocampal granular layer regulates the generation and the positioning of new granule neurons (Abe et al., 2018), as well as axonal elongation and sprouting (Pujol et al., 2005; Lysko et al., 2011; Su et al., 2012). According to its role in neurogenesis, the up-regulation of CXCL12 upon stroke (Wang et al., 2012), or demyelination (Carbajal et al., 2011; Patel et al., 2012; Williams et al., 2014) contributes to generate new cells and to restore normal CNS functions. Postnatal development of neurons in the cortical layer V depends on CX3CL1 signaling, which regulates the release of insulin-like growth factor (IGF-1) by microglia, important for survival of these neurons (Ueno et al., 2013). In addition, in the postnatal critical period, CX3CL1 signaling on microglia is important for the phagocytosis and removal of synaptic elements (Paolicelli et al., 2011), a mechanism important to refine neuronal connections (Zhan et al., 2014). The disruption of CX3CL1/CX3CR1 signaling in young rats decreases hippocampal neurogenesis, and CX3CL1 administration reverts the age-related decrease of hippocampal neurogenesis through IL-1β (Bachstetter et al., 2011). Neuronal progenitor cells (NPs) in the SVZ express CCR2 and migrate in response to monocyte chemoattractant protein 1 MCP1 (CCL2) gradient (Ji et al., 2004; Widera et al., 2004). However, while no alterations in neurogenesis have been reported in CCL2KO mice (Kiyota et al., 2013), a role for CCL2 in neurogenesis has been documented upon brain injury. In 2006 Belmadani et al. demonstrated that NPs engrafted in hippocampal slices could migrate towards area of inflammation/injury and this effect was CCL2/CCR2 dependent. CCL2 expression increased in glial cells in a mouse model of cerebral ischemia (transient MCAO), likely correlated with NPs migration towards the ischemic area (Yan et al., 2007). Impairing CCL2 signaling only affected post-ischemic neuroblast migration, not proliferation (Yan et al., 2007). CCL2 is also involved in NPs differentiation into neurons: Liu et al., 2007 reported that CCL2 increased the neuronal differentiation of NPs (measured as TuJ1-positive cells) without altering their proliferation. Finally, in a mouse model of Alzheimer disease, CCL2 deficiency affects the progressive neurocognitive dysfunctions, also reducing neurogenesis and differentiation in the subgranular zone (SGZ) of the dentate hippocampal gyrus (Kiyota et al., 2013).

Apart from neurons, chemokine signaling is also important in glia development. CXCL1 expressed by astrocytes and CXCR2 expressed by oligodendrocyte progenitor cells (OPC), drive the correct positioning of OPC in the spinal cord during development (Tsai et al., 2002), important for the maintenance of oligodendrocytes lineage and myelination (Padovani-Claudio et al., 2006). Moreover, CXCL1/CXCR2 signaling plays a role in OPC proliferation (Robinson et al.,

1998), also in response to injury, in postnatal spinal cord (Wu et al., 2000; Hosking et al., 2010). In vitro, CXCL12 regulates OPC migration and survival (Dziembowska et al., 2005). Furthermore, CXCL12 is determinant for the re-myelination of the corpus callosum in a mouse model of MS (Patel et al., 2010, 2012) and of the spinal cord in a mouse model of demyelination (Carbajal et al., 2011). Another chemokine involved in olygodendrocytic differentiation is CX3CL1 (Voronova et al., 2017). In the developing cortex, the CX3CL1 expressed by interneurons of the medial ganglionic eminence drives glial precursor cells differentiation into oligodendrocytes (Voronova et al., 2017). Moreover, authors speculated that CX3CL1, released by neurons, might represent a signal that contributes to oligodendrogenesis and myelination associated with neuronal activity (Gibson et al., 2014).

Chemokines affect synaptic transmission in several brain regions. Modulation of both glutamatergic and GABAergic neurotransmission, often with opposite effects, as well as regulation of neuronal excitability have been reported (Rostène et al., 2011a). Pioneer experiments demonstrated that IL8 and CXCL1 potentiate the spontaneous and evoked excitatory transmission in cerebellar neurons by increasing the cytosolic Ca^{2+} levels, whereas CXCL12 depresses the evoked input of the parallel fibers to Purkinje neurons (Giovannelli et al., 1998; Ragozzino et al., 1998, 2002). CXCL12 also induces a presynaptic increase of both glutamatergic and GABAergic neurotransmission onto serotoninergic neurons in the dorsal raphe, onto cortical immature neurons upon transient MCAO and onto dopaminergic neurons of substantia nigra (SN) (Guyon et al., 2006; Heinisch and Kirby, 2010; Ardelt et al., 2013). Post-synaptic modulation of GABA-A receptors has been reported for CX3CL1 onto serotoninergic neurons in the dorsal raphe and cortical neurons (Heinisch and Kirby, 2009; Roseti et al., 2013). At Schaffer's collateral-CA1 pyramidal neurons CX3CL1 depresses AMPA-mediated currents with a mechanism that involves inhibition of forskolin-induced Ser-845 GluR1 phosphorylation (Ragozzino et al., 2006), whereas it enhances NMDA-mediated neurotransmission via adenosine A2A subtype activation and D-serine release by glial cells (Maggi et al., 2009; Scianni et al., 2013). In the same area it has been reported that: i) CCL2 exerts pre-synaptic effects increasing the release of glutamate onto CA1 pyramidal neurons (Zhou et al., 2011); ii) CXCL16 enhances both the release of glutamate and GABA, requiring adenosine type 3 receptor (A3R) and microglia activation (Di Castro et al., 2016).

Effects on excitability have been also reported for CXCL12 onto vasopressin neurons in the hypothalamus and onto dopaminergic neurons in substantia nigra, the latter being mediated by modulation of high-threshold calcium currents (Callewaere et al., 2006; Skrzydelski et al., 2007; Guyon et al., 2008). CCL2 also modulates excitability of dopaminergic neurons in SN by closure of background channels, mainly selective to potassium ions, whereas on CA1 pyramidal neurons it increases excitability by enhancement of excitatory transmission (Guyon et al., 2009; Zhou et al., 2011).

Chemokines also play a role in the nociceptive process, modulating neuropathic pain through the cross-talk with opioid receptors (White et al., 2007; Mélik Parsadaniantz et al., 2015; Jayaraj et al., 2018), and modulate the functioning of the hypothalamus-pituitary axis being involved in the regulation of body temperature, feeding, water balance and stress responses (Rostène et al., 2011b). These huge amounts of evidence support a homeostatic modulatory role of chemokines in the adult CNS.

Chemokines and neuroprotection

CXCL12

As a potent chemoattractant for T- and B-lymphocytes and inflammatory monocytes, CXCL12 was long considered only a mediator of CNS inflammation (Calderon et al., 2006; Krumbholz et al., 2006; McCandless et al., 2008). However, the discovery that CXCL12 guides the homing of neuronal progenitor/stem cells into brain damaged regions, contributing to recovery both in ischemia and in neurodegenerative disorder, highlighted the neuroprotective effects of this chemokine (Robin et al., 2006; Li et al., 2012). Besides acting as a recruiting molecule, CXCL12 acts on cells of the brain parenchyma, such as neurons, astrocytes or microglia that do express its receptor CXCR4 (Meucci et al., 1998; van der Meer et al., 2000; Banisadr et al., 2002; Baudouin et al., 2006; de Haas et al., 2007; Reaux-Le Goazigo et al., 2012).

The first evidence that CXCL12 has effects on neurons and promotes neuroprotection were given by Meucci et al. (1998) when, for the first time, the authors demonstrated that CXCL12 reduced the apoptotic death of hippocampal neurons induced by gp120 or by glia deprivation. Following glia deprivation, neuroprotection was promoted by administration of CXCL12 specifically to neurons highlighting a direct activity of the chemokine on these cells. Further, stimulation of hippocampal neurons with CXCL12 was able to induce Akt phosphorylation and p65NF-kB nuclear translocation, both signaling implicated in pro-survival cell fate (Khan et al., 2004). Apoptotic cell death due to K^+ deprivation was also reduced by CXCL12 in primary cerebellar neurons, where it regulates the activity of cell-cycle proteins (Rb, E2F-1), involved in neuronal apoptosis (Khan et al., 2003). Accordingly, in primary cortical neurons, CXCL12 promotes Rb function increasing its expression, nuclear localization, and transcriptional activity and reducing the excitotoxic cell death due to NMDA receptors over-activation (Khan et al., 2008). In addition, CXCL12 promotes neuronal survival against gp120 neurotoxicity, increasing p53 acetylation and p21 expression (Khan et al., 2005). CXCL12 neuroprotection is also sustained by an increase in the pro-survival signaling of synaptic NMDA receptor, and in the down-regulation of the extrasynaptic NR2B-NMDA receptor subunit (whose activity is known to mediate neurotoxicity) (Nicolai et al., 2010). Since all the experiments presented in the above cited papers were performed using neuronal cultures with a separate astrocytes layer, it cannot be excluded that the neuroprotective effects might be also mediated by glial cells. Indeed, CXCL12 stimulates astrocytes promoting Akt phosphorylation (Khan et al., 2004), G-protein-PI-3Kinase-ERK1/2 signaling cascade leading to cell proliferation (Bajetto et al., 2001b), NF-Kb activation with consequent TNF-α (Han, 2001) and glutamate

release (Bezzi et al., 2001; Calì et al., 2008). In vivo, cerebral CXCL12 administration to ischemic animals has neuroprotective activity (Shyu et al., 2008). Accordingly, the over-expression (using adenoviral vector) of CXCL12, three days before but also one week after transient MCAO, reduced ischemic damage (Yoo et al., 2012). In line with these findings, in a permanent MCAO mouse model, virus-mediated over-expression of CXCL12 in the peri-infarcted area, one week after the insult, reduced brain atrophy and behavioral deficits, likely through Akt, ERK, P38 pathway, without eliciting inflammatory responses (Li et al., 2014).

Recently it has been reported that gliptin (Dipeptidyl-peptidase 4 DPP-4 inhibitor) improves motor functions and reduces tissue damage upon MCAO, increasing the cerebral level of CXCL12 (Chiazza et al., 2018). Since CXCR4 antagonist reduced gliptin induced functional recovery (Chiazza et al., 2018), it was speculated that CXCL12 represents an endogenous modulator counteracting brain damage. The upregulation and the release of CXCL12 from astrocytes was also observed in the ischemic penumbra (Stumm et al., 2002; Hill et al., 2004; Miller et al., 2005). In vitro, ischemia alters the expression of miRNAs associated with CXCL12 regulation, leading to increased CXCL12 expression and release from astrocytes (Shin et al., 2014). In addition, acting on microglial cells, CXCL12 activates signaling pathways that trigger the release of IL-6 (Lu et al., 2009), which has neuroprotective properties in ischemia (Loddick et al., 1998; Ali et al., 2000; Ohtaki et al., 2006).

Another novel neuroprotective activity of CXCL12/CXCR4 signaling has been identified in its ability to increase dendritic spine numbers (Pitcher et al., 2014). In particular authors found that, in opiate abuser and in neuroAIDS patients, deregulation of CXCL12/CXCR4 is determinant to cognitive dysfunction associated with dendritic spine loss. The authors also demonstrated that CXCL12/CXCR4 regulates dendritic spine density both in vitro, in pure neuronal cultures, and in vivo, in a rat model of opiate abuse.

CXCL12-CXCR4 signaling plays a role in neuroprotection also in Alzheimer disease: CXCL12 protected neurons from Aβ-induced apoptosis through the activation of Akt, ERK1/2 and the maintenance of metalloproteinase ADAM17 and, in vivo, counteracted the oxidative damage and the loss of spine density in the hippocampus (Raman et al., 2011). Furthermore, a decreased expression of CXCL12 was observed in the brain of Tg2576 and in 3XTg AD animal models at the stage of cognitive decline, as well as in brain tissue from AD patients (Parachikova and Cotman, 2007).

CX3CL1

CX3CL1 is a trans-membrane chemokine highly expressed by neurons and present in a soluble form upon cleavage by metalloproteases such as ADAM10, 17 (Garton et al., 2001; Hundhausen et al., 2003), catepsin-S and γ-secretases (Clark et al., 2007; Schulte et al., 2007; Fonovic et al., 2013). Both trans-membrane and soluble CX3CL1 forms bind a unique receptor CX3CR1, with possible differences in affinity and activity (Biber et al., 2007). The discovery of the specific expression of CX3CR1 in microglial cells (Cardona et al., 2006) opens to the perspective that CX3CL1 is implicated in neuron–microglia cross-talk and in the control of microglia activity (Biber et al., 2007). In 2000, Zujovic et al. reported for the first time that exogenous CX3CL1 restrained LPS-microglia activation in vitro, and that neutralization of endogenous CX3CL1 in hippocampal cultures increased the neurotoxic action on neuronal cells. Accordingly, in vivo neutralization of endogenous CX3CL1 potentiated LPS effects in the brain (Zujovic et al., 2000). Later, Mizuno et al. (2003) reported the reduction of IL-6, NO and TNF-α production by microglia stimulated with LPS upon CX3CL1 treatment, and a reduced neuronal cell death. Boehme et al. (2000) showed that CX3CL1 reduced FAS-mediated microglia cell death activating PI-3 kinase/PKB pathway, and modulating both the levels and the activation states of Bcl-2 family member proteins. In animal models, knocking down CX3CR1 signaling exacerbated microglia over-activation, increasing the release of IL-1β and apoptotic neuronal cell death in mice injected with LPS, and increased neuronal cell loss in PD and ALS mouse models (Cardona et al., 2006). In cx3cl1 −/− mice, the Adeno-Associated Virus (AAV)-mediated gene insertion of either soluble or membrane bound synthetic variant of CX3CL1 demonstrated that, in a MPTP- model of PD, only the soluble form rescued motor coordination, reduced neurodegeneration and microglia activation (Morganti et al., 2012). A role for endogenous CX3CL1 in the attenuation of a pro-inflammatory phenotype was also reported in a mouse model of Tauopathy (Lastres-Becker et al., 2014). Recent data show that only the over-expression of a specific cleavage variant of the soluble CX3CL1 reduced Tau-pathology (Finneran and Nash, 2019). In addition to restrain inflammatory microglia, other neuroprotective effects are mediated by CX3CL1 signaling. In hippocampal cultures, CX3CL1 reduced neuronal cell death due to gp120- or glutamate over-exposure (Meucci et al., 2000; Limatola et al., 2005). Microglial cells treated with CX3CL1 release soluble factors that promote neuroprotection in mixed hippocampal neuron–glia cultures. Among them adenosine modulates CX3CL1 neuroprotection through the activation of adenosine A1 receptor subtype (A1R) (Lauro et al., 2008, 2010). Acting on microglia, CX3CL1 indirectly modulates the activity of glutamate-transporter 1 (GLT-1) on astrocytes, with higher glutamate removal from the extracellular space, and this effect requires the function of A1R (Catalano et al., 2013). In a pMCAO rat model, i.c.v. injection of soluble CX3CL1, 30 min after ischemia, has long lasting protective effects, reducing lesion volume and neurological deficits, again with the involvement of active A1Rs (Cipriani et al., 2011).

CX3CL1-mediated neuroprotection and neuromodulation may also require the activity of adenosine-type 2 a receptors (A2ARs). Scianni et al. (2013) demonstrated that CX3CL1 modulates the NMDA glutamate receptor function and that this effect involves the release of D-serine from glial cells, and the activity of A2AR subtype. Altogether these data describe a mechanism by which CX3CL1, via A2AR and D-serine, and likely modulating synaptic NR2A/NMDARs, induced CREB phosphorylation, upregulation and release of BDNF, resulting in neuroprotection and neuromodulation (Lauro et al., 2015).

CXCL16

CXCL16 is another transmembrane chemokine that, upon cleavage by metalloproteases (ADAM 17, 10), can be released in a soluble form and stimulates its unique receptor CXCR6. Until recently, it was only known that, in the brain, CXCL16 levels increased upon inflammatory conditions, and that both microglia and astrocytes release CXCL16 (Ludwig et al., 2005). In patients affected by inflammatory disorders, such as MS, soluble CXCL16 is upregulated in the cerebrospinal fluid (CSF) (Le Blanc et al., 2006), and in the EAE mouse model CXCL16 plays a major role in recruiting immune cells, mainly neutrophils, across the BBB (Wojkowska et al., 2014). All these data suggest a specific role of CXCL16 in mediating neuro-inflammatory and neurotoxic events in the brain. However, its constitutive expression in different CNS cells (Ludwig et al., 2005; Rosito et al., 2012) suggests additional roles in mediating cell-to-cell communication. In vitro experiments, by Rosito et al. (2012), demonstrated that in mixed hippocampal neuron-glia cultures the administration of soluble CXCL16 led to neuroprotection against glutamate-excitotoxicity and oxygen glucose deprivation (OGD) insults. Specifically, CXCL16 acts on astrocytes to induce the release of soluble mediators that concur to neuroprotection, with a mechanism that requires functional activity of Adenosine A3 Receptor subtype (A3R). One of these mediators is the chemokine CCL2, since the neutralization of soluble CCL2 reduced the protective effect of CXCL16 (Rosito et al., 2012). Further, i.c.v. injection of soluble CXCL16 in a pMCAO mouse model reduced ischemic brain damage in wt mice but was less effective in A3R −/− mice (Rosito et al., 2014). The observation that in cxcr6 −/− mice the ischemic lesion was significantly increased compared to wt animals suggests that endogenous CXCL16/CXCR6 signaling is important to counteract brain damage. Furthermore, CXCL16 was upregulated in hippocampal cultures upon recovery from OGD, and in the ipsilateral ischemic hemisphere in pMCAO animals leading to the hypothesis that the release of CXCL16 is an attempt of the brain to limit neuronal damage (Rosito et al., 2014). In chronic or acute neurodegenerative diseases, both excitotoxicity (Lipton, 2005; Hallett and Standaert, 2004; Shaw et al., 1995; Castillo et al., 1996; Zauner et al., 1996), and neuroinflammatory conditions exacerbate brain damage and dysfunction (Ransohoff, 2016). Considering the key role of microglia in sensing neuronal microenvironment (Davalos et al., 2005), it was not surprising to discover that some of the effects of CXCL16 are also mediated by these cells. Recently, Lepore et al. (2018) demonstrated that primary microglial cells respond to CXCL16 stimulation acquiring an anti-inflammatory phenotype and, in the context of an inflammatory environment (LPS-IFNγ), CXCL16 attenuates the pro-inflammatory microglia phenotype, thus suggesting a role in contrasting neuroinflammation.

CCL2

Although CCL2 plays a key role in leucocyte transmigration across the blood–brain barrier (Weiss et al., 1998) promoting brain inflammation (Chang et al., 2016; Varvel et al., 2016; Cédile et al., 2017), other reports indicated that high levels of CCL2 in the brain are not directly correlated with inflammation (Kolb et al., 1999; Little et al., 2002).

The first evidence of a neuroprotective activity of CCL2 against NMDA toxicity in mixed cortical cultures were presented by Bruno et al. (2000). They reported that CCL2 was neuroprotective at different doses when applied before or during the toxic insult, suggesting that receptors with different affinity could be involved. CCL2 also reduced apoptotic cell death induced by NMDA and tat-protein in human mixed neuron-astrocytes cultures (Eugenin et al., 2003). The authors found that CCL2 reduced the extracellular level of glutamate and the intracellular trafficking of tat and NMDA receptor 1 in neurons. In addition, they found that CCL2, applied after the toxic insult, did not induce neuroprotection, suggesting that CCL2 is required as an early signal in neurons and/or astrocytes. The release of CCL2 by astrocytes also mediates the neuroprotective effects of RANTES against tat toxicity (Eugenin et al., 2003), and the neuroprotective effects of noradrenaline against NMDA excitotoxicity and OGD damage (Madrigal et al., 2009). The mechanism of this protective activity was investigated in midbrain primary neuronal cultures (Yao et al., 2009). The authors reported that CCL2 stimulates the PLC/IP3R pathway which, in turn, activates the transient receptor potential channel (TRPC), with consequent increase of intracellular calcium. Calcium elevation triggers the MEK/ERK pathway, leading to CREB activation and neuronal survival. In addition, CCL2 activates PI3K/Akt/NF-kB pathway, which also potentiates neuronal survival.

CXCL12/CX3CL1/CXCL16/CCL2: a quartet of endogenous modulators that drive neuron–glia communication to counteract brain damage

Awareness that self-endogenous protective mechanism can act in the brain to counteract or restrain toxic insult derives from the concept of tolerance and preconditioning in ischemia, where precondition is able to trigger endogenous protective mechanisms that limit the effects of subsequent injuries (Stevens et al., 2014). Although the activation of destructive pathways induces cell death, the induction of simultaneous protective mechanisms limits the resulting damage and set the stage for tissue repair and reorganization in ischemia (Iadecola and Anrather, 2011).

Damaged neurons respond to neurotoxic insults releasing soluble factors that can be sensed by surrounding glia: one of this factors is CX3CL1, that is upregulated (Tarozzo et al., 2002; Zhu et al., 2009), cleaved and released from neurons upon ischemia, excitotoxic insult and traumatic brain injury (Chapman et al., 2000; Limatola et al., 2005; Noda et al., 2011; Gaetani et al., 2013). In addition, the upregulation and release of CXCL12 from astrocytes has been reported in the ischemic penumbra upon ischemic insult (Hill et al., 2004; Miller et al., 2005; Shin et al., 2014). Recently CXCL16 has been found to be over-expressed following pMCAO and in in vitro OGD (Rosito et al., 2014), and increased CCL2 expression after brain ischemia has been reported (Kim et al., 1995; Wang and Feuerstein, 1995; Guo et al., 2014).

Since, as reported in this review, all the cited chemokines can trigger different mechanisms of neuroprotection, limiting apoptotic and excitotoxic cell death as well as inflammatory conditions, it can be speculated that upon noxious insult endogenous protective programs, such as the chemokine-induced-chemokine release, might orchestrate neurons-microglia-astrocytes action to preserve and limit brain damage.

It has been shown that in neurons CXCL12 triggers intracellular pathways (Khan et al., 2005, 2008) that can up-regulate the transcription of cx3cl1 gene such as NF-Kb and p53 (Shiraishi et al., 2000). Cook et al. (2010) showed that CXCL12 increases the shedding of neuronal CX3CL1, likely via up-regulation of neuronal ADAM17, suggesting that, in addition to the direct neuroprotective activity of CXCL12, its ability to induce CX3CL1 release may further facilitate neuronal recovery after excitotoxic insults. CX3CL1, in turn, can elicit the release of soluble CXCL16 from astrocytes and microglia, and A3R and CCL2, mediators of CXCL16 neuroprotective activity, represent active player in CX3CL1 protection against excitotoxic-insult (Rosito et al., 2012). In line with these data, the neuroprotection induced by CX3CL1 against ischemic insult is significantly reduced in mice that lack CXCL16 signaling (Rosito et al., 2014).

The above mentioned findings strongly corroborate the concept that, in the CNS, chemokines could represent key endogenous modulators of the cross-talk between neurons and glia cells aimed at preserve brain functioning (Fig. 1).

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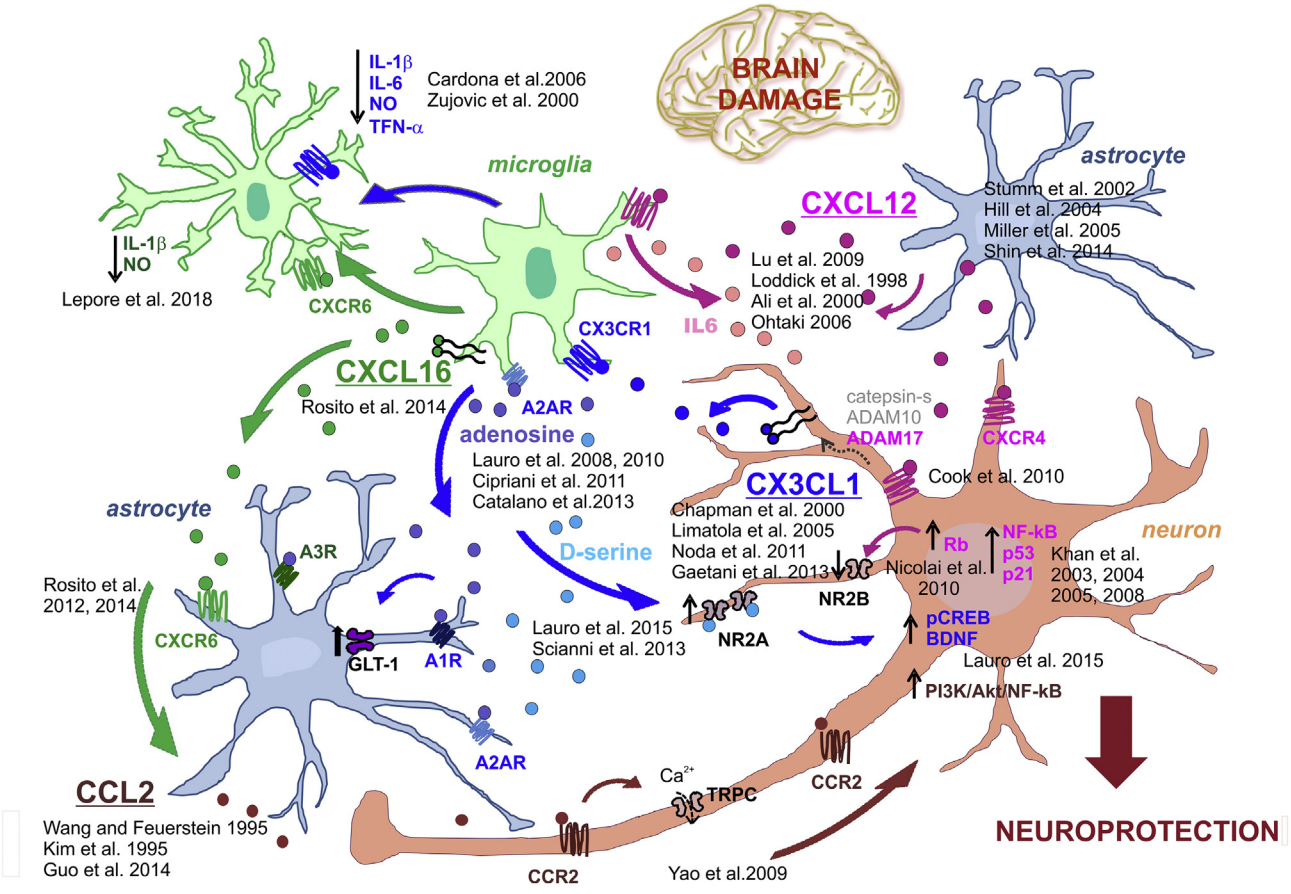

Fig. 1. Summary of the main effects orchestrated by CXCL12/CX3CL1/CXCL16/CCL2 on astrocytes, microglia and neurons to counteract brain damage. The effects of CXCL12 (pink), CX3CL1 (blu), CXCL16 (green), and CCL2 (brown) are depicted.As reported in the text, following ischemia astrocytes release CXCL12 that promotes neuroprotection directly acting on neurons and modulating pro-survival pathways (NF-kB, p53, p21); reducing neuronal apoptosis regulating cell cycle protein (Rb) and regulating NMDA (NR2B) receptor subunits. Acting on microglia CXCL12 induces the release of IL-6 that contributes to neuroprotection. CXCL12 also promotes the neuronal shedding of CX3CL1 by ADAM17 (Pink pathway).Damaged neurons release CX3CL1 that acts on microglia to reduce cell activation and to release adenosine. CX3CL1 and adenosine modulate GLT-1 activity on astrocytes with a mechanism dependent on A1R activity, and induce the release of D-serine from glial cells depending on A2AR activity. CX3CL1 and D-serine modulate neuronal NR2A-NMDA receptor functions, and induce the up-regulation of pro-survival pathways such as pCreb and BDNF. CX3CL1 also promotes the release of CXCL16 from glia (Blu pathway).CXCL16 is upregulated upon brain damage. With a mechanism that requires the activation of A3R, CXCL16 induces astrocytic release of CCL2, important to mediate neuroprotection. In addition CXCL16 contrasts microglia polarization towards inflammatory phenotypes (Green pathway). CCL2, is upregulated upon ischemia, and directly acts on neurons leading to activation of pro-survival pathways via TRPC channels, or via PI3K/Akt/NF-kB (Brown pathway).All these mechanisms contribute to neuroprotection.

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