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Review article

The role of monocyte chemoattractant protein MCP1/CCL2 in neuroinflammatory diseases

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ABSTRACT

Inflammatory response represents one of the first immune processes following injury. It is characterized by the production of various molecules that initiate the recruitment of immune cells to the lesion sites, including in the brain. Accordingly, in acute brain trauma, such as stroke, as well as during chronic affections like multiple sclerosis or Alzheimer's disease, inflammation occurs in order to "clean up" the lesion and to limit its area. Nevertheless, prolonged and sustained inflammation may have cytotoxic effects, aggravating the incidence and the severity of the disease. Among molecules produced during inflammation associated to neuronal death, monocyte chemoattractant proteins (MCPs) seem to be particularly important. This review will focus on the current knowledge about one of the MCPs, CCL2, and its cognate receptor, CCR2, both expressed in physiological conditions and during neurodegenerative diseases.

Contents

1. Introduction

For a long time, central nervous system (CNS) diseases have been categorized as inflammatory and noninflammatory disorders. In recent years, our understanding of the neuropathologies has made major advances and it is now acknowledged that inflammation plays a major

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role in many chronic and acute pathological conditions. Particularly, many evidences demonstrate that inflammation and inflammatory mediators contribute to such CNS disorders (for review Lucas et al., 2006). Historically, acute and chronic neuroinflammatory processes were first studied in diseases such as meningitis or multiple sclerosis (MS) which present aspects of neurodegeneration. More recently, evidences were given that inflammation may also alter the disease course in acute stroke-mediated neurodegeneration and progressive degenerative disorders such as Alzheimer's disease (AD) or Parkinson's disease (PD).

Chemokines, which are involved in the chemoattraction of cells, especially those of the immune system are some of the most important inflammatory factors (for review Bajetto et al., 2001). In the CNS, they are involved in the recruitment of the main resident immune cell types of the brain (astrocytes and microglia) and of infiltrating monocytes from the systemic bloodstream (Rollins, 1996). They can be produced by different cells types including glial and neuronal cells. Both cell types express chemokine receptors, shown to modulate neuronal activity, and even, being neurotoxic. Thus, chemokines may have a dual action, by acting on immune cells (attraction and activation) and on neurons (modulation of activity and survival).

During neurodegenerative diseases, monocytes and microglia are some of the most recruited immune cells at the lesion site in the CNS. Monocyte chemoattractant proteins (MCPs), which belong to the beta chemokine family, and especially CCL2 (MCP1) and its receptor CCR2 have been implicated in the previously cited neurological disorders. With respect to chronic neuroinflammation, a critical role for CCL2 has been established in animal models for MS. In acute neuroinflammation, experimental evidence for a detrimental role of CCL2 in stroke and excitotoxic injury has been found. Besides, AD is characterized by senile plaques surrounded by many activated immune cells producing a large number of inflammatory-related molecules such as cytokine and chemokines, among them CCL2.

Following the presentation of the known functions of CCL2 in healthy CNS, this review will focus on the role of CCL2 in pathological mechanisms associated to neuroinflammatory diseases. Particular emphasis will be given on MS, the first described model of neuroinflammatory related disease of the CNS, stroke as an example of acute pathology and the well documented AD, since it is the most prevalent progressive degenerative disorders.

2. The monocyte chemoattractant proteins family

Chemokines are a family of small proteins consisting of 60 to 100 amino acids with 20 to 90% homology in their sequences. They constitute a class of chemoattractant cytokines which are subdivided into four families based on the number and spacing of the conserved cysteine residues in the N-terminus of the protein. They are named C, CC, CXC, and CX3C, according to the systematic nomenclature. The monocyte chemoattractant proteins constitute an important group within the CC-chemokine sub-family. MCP1 was the first discovered and remains the best characterized but the five MCPs share 60–70% sequence homology and structural similarity. Later on, the MCPs were reclassified as CCL2 (MCP1), CCL8 (MCP2), CCL7 (MCP3), CCL13 (MCP4) and CCL12 (MCP5) (Bacon et al., 2002). Their classification and nomenclature can be found in reviews (Murphy, 2002; Floridi et al., 2003; Rostène et al., 2007).

2.1. The CCR2 receptor

The biological effects of chemokines are mediated via specific G-protein-coupled receptors (Ransohoff, 2002). Most chemokine receptors can be stimulated by several chemokine. Indeed, the chemokine receptor CCR2 binds the five pro-inflammatory MCPs: CCL2, CCL8, CCL7, CCL13 and CCL12 (Gong et al., 1997; Wain et al., 2002; Gouwy et al., 2004). CCL2 is the most potent at activating signal transduction pathways leading to monocyte transmigration (Sozzani et al., 1994). There are two alternatively spliced forms of CCR2 namely CCR2A and CCR2B which differ only in their carboxy-terminal tails (Charo et al., 1994). It is shown that CCR2A and CCR2B can activate different signaling pathways and exert different actions, but the dominant form is CCR2B, which accounts for 90% of the CCR2 expressed on the cell-surface (Van Coillie et al., 1999). Targets of CCR2 signaling include phosphatidylinositol-3-OH kinase (PI3K), mitogen activated protein kinases (MAPK) and protein kinase C (Thelen, 2001; Lu et al., 2003; Wain et al., 2002), indicating a wide range of intracellular pathways may be involved in cellular responses elicited by CCL2.

2.2. The CCL2/CCR2 network in the brain

The expression of the chemokine system differs in the CNS providing insights into the processes required for normal immune surveillance and pathological immune-mediated effector conditions. CCL2 mediates its effects through its receptor CCR2, and unlike CCL2, CCR2 expression is relatively restricted to certain types of cells. CCR2 is constitutively expressed by immune cell types, including monocytes, activated T cells, and dendritic cells (Van Coillie et al., 1999). CCR2 expression has been reported in cultured rat microglia (Boddeke et al., 1999) and in human fetal astrocytes (Andjelkovic et al., 2002). CCR2 is also expressed in neurons of the adult rat brain as described in Fig. 1. Neuronal expression of CCR2 is mainly found in the anterior olfactory nucleus, cerebral cortex, hippocampal formation, caudate putamen, globus pallidus, paraventricular and supraoptic hypothalamic nuclei, amygdala, substantia nigra, ventral tegmental area and in brainstem and cerebellum (Banisadr et al., 2005b). CCR2 co-localization with classical neurotransmitters was also observed in dopaminergic and cholinergic neurons (Banisadr et al., 2005b). The constitutive neuronal CCR2 expression in selective brain structures suggests that this receptor could be involved in neuronal communication and possibly associated to dopaminergic and cholinergic neurotransmission and related disorders.

Several studies have demonstrated that CCL2 are not only expressed in neuroinflammatory conditions but are also constitutively present in the brain in both glial cells (Barna et al., 1994; Berman et al., 1996; Glabinski et al., 1996; Hanisch, 2002) and neurons (Banisadr et al., 2005a) as described in Fig. 1. The fact that they are expressed at a low concentration in discrete neuroanatomical regions suggests that they may act as modulators of neuronal functions (for review Rostène et al., 2007). The neuronal expression of CCL2 is mainly found in the cerebral cortex, globus pallidus, hippocampus, paraventricular and supraoptic hypothalamic nuclei, lateral hypothalamus, substantia nigra and in Purkinje cells in the cerebellum. In addition, immunohistochemical

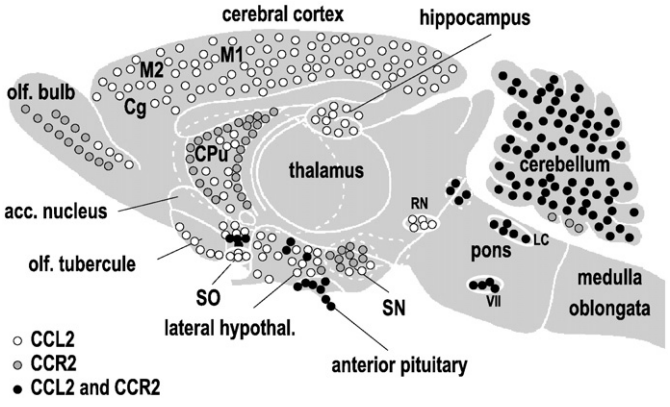

Fig. 1. Neuroanatomical localization of CCL2 (white circles) and its receptors (gray circles) in the normal adult rat brain. In a number of regions the distribution of the chemokine and its receptor overlap (black circles). VII: facial nucleus, acc. nucleus: accumbens nucleus, Cg: cingulated gyrus, CPu: caudate putamen, lateral hypothal.: lateral hypothalamus, LC: locus coeruleus; M1: primary motor area of the cortex, M2: secondary motor area of the cortex, Olf bulb: olfactory bulb, RN: red nucleus, SN: substantia nigra, SO: suraoptic nucleus. Adapted with permission from Rostène et al., Nature reviews 2007.