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The chemokine receptor CCR5 in the central nervous system

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ABSTRACT

The expression and the role of the chemokine receptor CCR5 have been mainly studied in the context of HIV infection. However, this protein is also expressed in the brain, where it can be crucial in determining the outcome in response to different insults. CCR5 expression can be deleterious or protective in controlling the progression of certain infections in the CNS, but it is also emerging that it could play a role in non-infectious diseases. In particular, it appears that, in addition to modulating immune responses, CCR5 can influence neuronal survival. Here, we summarize the present knowledge about the expression of CCR5 in the brain and highlight recent findings suggesting its possible involvement in neuroprotective mechanisms.

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1. Introduction

Chemokines are small proteins (70–90 aminoacids), divided into four different groups according to the position of conserved cysteines (C) in their sequence: CXC or alpha, CC or beta, C or gamma and CXC3 or delta chemokines (Rossi and Zlotnik, 2000). The word "chemokine" is derived from their function as chemotactic cytokines, resulting in activation and migration of leukocytes toward sites of inflammation. This process is mediated

Abbreviations: CNS, central nervous system; CC, chemokine receptor 5 (CCR5); CSF, cerebrospinal fluid; HIV, human immunodeficiency virus; MIP-1α, macrophage inflammatory protein 1 alpha; MIP-1β, macrophage inflammatory protein 1 beta; RANTES, regulated on activation T cell expressed and secreted; TBE, tick-borne encephalitis; WNV, West Nile virus.

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by the interaction of chemokines with their respective chemokine receptor. There have been 50 chemokines and 20 chemokine receptors identified to date (Domanska et al., 2010).

Chemokine receptors belong to the seven transmembrane G-protein-coupled receptor (GPCR) family. Receptor nomenclature is derived from their binding of chemokines: CC chemokines bind to CC receptors (CCR), CXC chemokines to CXCRs, and similarly for C and CX3C receptors. Within one subfamily, usually more than one chemokine can activate a given chemokine receptor, but in a few cases specific receptor/ligand pairs have been documented (Domanska et al., 2010).

Expression and activation of chemokine receptors is mostly related to the control of leukocyte migration. However, chemokine receptors also participate in the regulation of many other physiological and pathological processes, such as angiogenesis or metastasis formation (Rossi and Zlotnik, 2000). Also, there is increasing evidence for a role of chemokine receptors in the central nervous system (Bajetto et al., 2001; Cartier et al., 2005; Rostene et al., 2007).

The CCR5 chemokine receptor is mainly expressed in memory and effector T-lymphocytes, NK cells, monocytes, macrophages and immature dendritic cells. In these cell types it regulates chemotaxis and cell activation (Balistreri et al., 2007; Mueller and Strange, 2004; Oppermann, 2004), through the interaction with the following β-chemokines: CCL3 (MIP-1alpha), CCL4 (MIP-1beta), CCL5 (RANTES), CCL8 (MCP-2), CCL11 (eotaxin), CCL14a (HCC-1), CCL16 (HCC-4) (Alexander et al., 2008).

In 1996, five groups from different laboratories published at the same time their studies showing that the chemokine receptor CCR5 is a major co-receptor for the entry of HIV (human immunodeficiency virus) into target cells (Alkhatib et al., 1996; Choe et al., 1996; Deng et al., 1996; Doranz et al., 1996; Dragic et al., 1996). The interest for CCR5 was sparked by the discovery that a particular allelic alteration in the human CCR5 gene provided protection against HIV infection. Indeed, it was observed that some individuals had remained uninfected in spite of multiple exposures to HIV (Clerici et al., 1992; Langlade-Demoyen et al., 1994; Rowland-Jones and McMichael, 1995). The careful analysis of the CCR5 gene in isolated $CD4^+$ T cells led to the discovery of a 32 base pair deletion (CCR5Δ32), which results in a truncated protein (215 instead of 352 amino acids), thought to be devoid of intrinsic activity (Samson et al., 1996b). Indeed, the deletion spans nucleotides 794–825 corresponding to the second extracellular loop of the receptor, which precludes membrane insertion of the mutant protein (Liu et al., 1996). Individuals carrying both alleles of this mutation do not show any particular phenotype, appear healthy and are significantly protected from HIV, due to the virus not being able to access its co-receptor CCR5 for cellular entry. Although heterozygous individuals can be infected by HIV, the progression of infection is slower and their viral load is decreased (Liu et al., 1996; Samson et al., 1996b). These discoveries have focused research on the mechanisms of activation, signalling and function of this particular chemokine receptor, motivated by the potential discovery of drugs targeting CCR5 for use as HIV therapies.

Despite the beneficial effect of CCR5-deficiency in the case of HIV infection, other consequences of the absence of CCR5 have not been fully elucidated, especially concerning possible adverse effects in the central nervous system (CNS). Indeed, increasing evidence indicates the expression of chemokines and their receptors in the CNS. It appears that chemokines are involved in brain development, neuronal signalling and synaptic transmission (reviewed in Bajetto et al., 2001; Cartier et al., 2005; Domanska et al., 2010; Rostene et al., 2007). Similarly, immunohistochemical and *in vitro* studies have revealed a constitutive expression of CCR5 in the CNS; however its function in the brain is still poorly understood. Furthermore, recent studies have proposed that a non-functional CCR5 receptor could influence response to CNS pathologies and even confer a certain vulnerability to the progression of particular diseases.

In this review, we summarize the present data concerning the distribution and the physiological functions of CCR5 in the CNS, and its involvement in neurological diseases.

1.1. The CCR5 gene: structure, regulation and species similarities

The CCR5 gene is located on chromosome 3p21 (Liu et al., 1996) and consists of 4 exons and only 2 introns. Exon 4 contains the open reading frame, but a complex splicing in the 5′-UTR and in the 4 exons leads to multiple CCR5 transcripts (Mummidi et al., 1997). The gene codes for a protein consisting of 352 amino acids, with a resulting molecular mass of 40.6 kDa (Samson et al., 1996a). Transcription is regulated by two different promoters, which are upstream and downstream of exon 1 (Mummidi et al., 1997). The downstream promoter includes the 'intronic' region between exons 1 and 3. It contains a pair of consensus TATA elements and potential binding sites for several transcription factors, such as STAT, NF-κB, AP-1, NF-AT, and CD28RE (Liu et al., 1998). The transcriptional regulation of the CCR5 gene seems to be cell specific and there are data indicating that NFκB subunits (Bream et al., 1999; Liu et al., 1998) and/or the cAMP/CREB pathways (Kuipers et al., 2008) are mainly involved. A strong homology has been described between the 5′-UTR of the human CCR5 and that of mouse and rat, suggesting similarly conserved regulatory regions. Concerning the coding sequence, human CCR5 has 82% homology with the mouse (Boring et al., 1996) and 98% with the rhesus (Margulies et al., 2001). Despite these differences, human β-chemokines CCL3, CCL4, and CCL5 show very similar IC^{50} values for the human rhesus and mouse CCR5 receptor (Saita et al., 2007).

By contrast, small organic molecule antagonists developed for the human CCR5 receptor (see also below) appear to be species-specific. This is true for TAK-779, an experimental compound, which shows similar affinity for rhesus and human CCR5, but only a very low affinity for the murine CCR5 receptor (Saita et al., 2007). In the same way, the CCR5 antagonist maraviroc, used for HIV therapy has at least 1400-fold lower affinity interaction for the mouse, rat and dog CCR5 (Pfizer, 2007).

1.2. CCR5 variants in humans: focus on the CCR5Δ32 deletion

Several allelic variants of the CCR5 gene have been identified in different populations (Ansari-Lari et al., 1997; Carrington et al., 1997). These mutations occur in both the coding sequence and the promoter region (Kostrikis et al., 1999; McDermott et al., 1998), and are able to alter either the extent of transcript expression (McDermott et al., 1998) or the functionality of the receptor (Blanpain et al., 2000). However, the most known and studied mutation is the deletion of 32 base pairs in the coding sequence; this polymorphism has a surprisingly high frequency in certain populations.

Approximately 10% of the Caucasian population is heterozygous for the CCR5Δ32 mutation and 1–2% is homozygous (Libert et al., 1998; Martinson et al., 1997). This allele displays a particular geographic distribution. In fact, it is common almost exclusively in Caucasians, with the highest allele frequencies present among North eastern European populations (Finnish, Icelandic and Mordvinian around 16%), and the lowest in the South of Europe.

The origins of this mutation and the reasons for its particular geographic distribution have been the subject of many studies. Multiple evidences indicate that the CCR5Δ32 allele probably arises from a unique mutation event (Galvani and Novembre, 2005; Libert et al., 1998). It has been further hypothesized that this