CXCR1 (chemokine (C-X-C motif) receptor 1)

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Abstract: Review on CXCR1, with data on DNA/RNA, on the protein encoded and where the gene is implicated.

Identity

Other names: C-C, C-C-CCKR-1, CD128, CD181, CDw128a, CKR-1, CMKAR1, IL8R1, IL8RA, IL8RBA

HGNC (Hugo): CXCR1

Location: 2q35

Local order: Orientation: minus strand.

Note
CXCR1 together with IL8RB, another high affinity IL-8 receptor, and its pseudogene (IL8RBP), form a gene cluster in chromosome 2q33-q35 (provided by RefSeq, Jul 2008).

DNA/RNA

Description
The CXCR1 gene (il8ra) is 4149 bp long and is composed of two exons, one of them included in the coding region (1053 bp) CXCR1 has 165 known SNPs; many of them correlate with disease states.

Genetic locus: CXCR1, together with its homolog CXCR2 (76% amino acids identity) and its pseudogene (il8rp), reside in chromosome 2q34-35. The high homology and close chromosomal localization between the three genes suggest gene duplications.

Transcription

Transcripts: primer extension analysis revealed two start sites for CXCR1 (Sprenger et al., 1995). In addition, neutrophils contain two transcripts of CXCR1 (2.0 and 4.0 kb) which result from the usage of alternative polyadenylation signals.

Transcription regulators: PU.1, which belongs to the ets family of transcription factors, is a major activator of CXCR1 expression (Wilkinson and Navarro, 1999). HIF1 and NF-kappaB mediate the transcription of CXCR1 under hypoxia in prostate cancer cells (Maxwell et al., 2007).

CXCR1 mRNA expression is also regulated by G-CSF (Lloyd et al., 1995).

Pseudogene

Conservation during evolution: the CXCR1 gene was present in the common ancestor of chordates and has orthologs in diverse species, from lizards and Xenopus to primates.

There is a high level of homology between CXCR1 from human, rabbit, rat, and mouse. The sequencing of the coding region of CXCR1 in worldwide human populations and 5 representative nonhuman primate species revealed accelerated protein evolution in the human lineage, mainly at the N-terminal ligand/receptor recognition domain (Liu et al., 2005).

**Figure 1.**

**Protein**

**Description**
350 amino acids, 39,791 Da.
CXCR1 is a G protein coupled receptor (GPCR), composed of seven transmembrane (TM) helices, an N-terminal ligand binding domain and a signaling cytoplasmic tail.

**Expression**
Expression in tissues: according to SAGE (serial analysis of gene expression), CXCR1 is mainly expressed in the bone marrow, retina, heart, lungs and in the placenta.
Expression in cell types: CXCR1 is expressed on a wide variety of cell types, including neutrophils, monocytes, CD8 T cells, mast cells, basophils, natural killer cells, keratinocytes, fibroblasts, neurons, endothelial cells, and melanocytes.
Expression regulators: CXCR1 was found to be up-regulated by IL6, by a yet-unknown mechanism (Eikawa et al., 2010).

**Localisation**
CXCR1 resides in the plasma membrane and transduces signals into the cell (figure 1).

**Function**
Upon binding to its ligands, CXCR1 transduces signals via the phosphatidylinositol-calcium second messenger system and plays an important role in acute inflammation. IL-8 (CXCL8), the main ligand of CXCR1, is a powerful neutrophil chemotactic factor and its binding to CXCR1 induces activation and migration of neutrophils (Holmes et al., 1991; Liu et al., 2005).
In neutrophils, receptor activation also stimulates the release of granule enzymes and the generation of superoxide in respiratory burst (Jones et al., 1996).
In addition to its effect on immune cells, CXCR1 may be important in regulating vasculogenesis and consequent tumor growth (Strieter et al., 1995).
The signaling pathway of CXCR1 as a G protein coupled receptor is presented in figure 1. Noteworthy, CXCR1 signaling also activates monomeric, low molecular weight G proteins of the Ras and Rho families (Laudanna et al., 1996).
Ligand selectivity: CXCR1 displays a relatively narrow selectivity and high preference for IL-8. At low affinity it also binds MGSAXRO.

**Implicated in**

**Melanoma**

**Note**
Highly expressed by melanoma cells and mediates their proliferation and invasiveness in vitro and tumor growth in mice experiments (Singh et al., 2009). Recently, it was shown as a potential target for T cell engineering, a finding which highly impacts on adoptive cell immune-therapy for melanoma patients (Sapoznik et al., 2012).
Breast cancer

Note
CXCR1 is over-expressed in tumor and cascular endothelial cells, as shown by immunohistochemistry studies on a cohort of 50 breast cancer patients performed by Miller et al. (Miller et al., 1998). Recently, Singh and his colleagues showed that CXCR1 as well as CXCR2 are important mediators of breast cancer stem-like cells activity. Furthermore, blockade of CXCR1 and CXCR2 adds to the inhibitory effect of HER2-targeted therapy on these cells and may potentially serve as a novel therapeutic strategy for breast cancer (Singh et al., 2013).

Colorectal cancer

Note
CXCR1 is over-expressed in colorectal cancer cells (Abolhassani et al., 2008) and antagonists of CXCR1 and CXCR2 inhibit liver metastases of human colon cancer in a murine model (Varney et al., 2011). Interestingly, based on two large cohorts of population incident studies, Bondurant and his colleagues were recently able to show that SNPs in genes connected with the IL8 pathway (including CXCR1 and CXCR2) are associated with higher risk of both colon and rectal cancers (Bondurant et al., 2013).

Prostate cancer

Note
CXCR1 is over-expressed in tumor cells from human prostate biopsies (Murphy et al., 2005). Depletion of CXCR1 by RNA interference in androgen-independent human prostate cancer cells induces cell death and reduced proliferation in vitro (Shamaladevi et al., 2009).

In consistence with that, down-regulation of CXCR1 by shRNA or by a specific antagonist lead to inhibition of human xenograft growth in immune-deficient mice (Shamaladevi et al., 2009; Liu et al., 2012).

Nasopharyngeal carcinoma

Note
Immune-histochemical analysis of 30 patients with nasopharyngeal carcinoma proved that its expression in tumor tissue significantly correlates with a shorter overall survival rate. Thus it is an indicator of poor prognosis in nasopharyngeal carcinoma (Horikawa et al., 2005).

Chronic obstructive pulmonary disease (COPD)

Note
CXCR1 polymorphisms are identified polymorphisms associated with COPD and asthma, as shown by Stemmler et al. by screening 50 COPD patients (Stemmler et al., 2005).

Pignatti and colleagues found that neutrophilic asthma patients have similar expression levels of CXCR1 as COPD patients and that CXCR1 expression is negatively correlated with the inflammatory infiltrate in the airways (Pignatti et al., 2005).

Urinary tract infection recurrent

Note
CXCR1 was first identified as a candidate gene for urinary tract infections when Godaly et al showed that mIL-8R mutant mice developed acute pyelonephritis with severe renal scattering (Godaly et al., 2001). Lundstedt et al. have afterwards identified two sequence variants which were shown to impair transcription of CXCR1 and led to reduced levels of the CXCR1 protein in children prone to urinary tract infections (Lundstedt et al., 2007).

Psoriasis

Note
A single study by Arenberger et al showed in a small cohort of psoriasis patients that CXCR1 is slightly though significantly over-expressed in polymorphonuclear leukocyte infiltration in the epidermis as compared to normal volunteers (Arenberger et al., 1992).

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