Atlas of Genetics and Cytogenetics in Oncology and Haematology

OPEN ACCESS JOURNAL INIST-CNRS

Gene Section

Review

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

Sivan Sapoznik, Stav Kozlovski, Gal Markel

The Ella Institute for Melanoma Research and Treatment, Cancer Research Center, Sheba Medical Center, Israel (SS), The Ella Institute for Melanoma Research and Treatment, Cancer Research Center, Sheba Medical Center, Israel and Clinical Microbiology and Immunology, The Sackler School of Medicine of the Tel Aviv University, Israel (SK), The Ella Institute for Melanoma Research and Treatment, Cancer Research Center, and Talpiot Medical Leadership Program, Sheba Medical Center, Israel and Clinical Microbiology and Immunology, The Sackler School of Medicine of the Tel Aviv University, Israel (GM)

Published in Atlas Database: June 2013

Online updated version : http://AtlasGeneticsOncology.org/Genes/CXCR1ID40966ch2q35.html
DOI: 10.4267/2042/52070

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-CKR-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-q36 (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 poly adenylation 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).

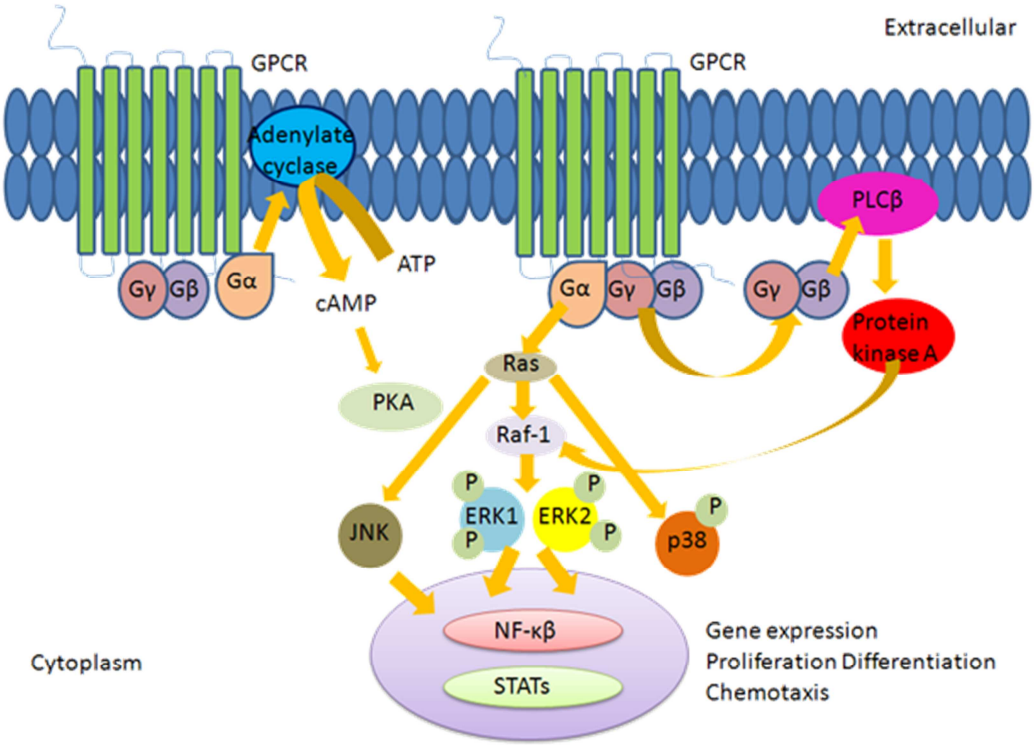

Figure 1.

Protein

Description

350 amino acids, 39791 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 MGSA/GRO.

Implicated in

Melanoma

Note

Highly expressed by melanoma cells and 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 obstractive 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-8Rh mutant mice developed acute pyelonephiritis 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).

References

Holmes WE, Lee J, Kuang WJ, Rice GC, Wood WI. Structure and functional expression of a human interleukin-8 receptor. Science. 1991 Sep 13;253(5025):1278-80

Arenberger P, Kemény L, Süss R, Michel G, Peter RU, Ruzicka T. Interleukin-8 receptors in normal and psoriatic polymorphonuclear leukocytes. Acta Derm Venereol. 1992 Sep;72(5):334-6

Lloyd AR, Biragyn A, Johnston JA, Taub DD, Xu L, Michiel D, Sprenger H, Oppenheim JJ, Kelvin DJ. Granulocyte-colony stimulating factor and lipopolysaccharide regulate the expression of interleukin 8 receptors on polymorphonuclear leukocytes. J Biol Chem. 1995 Nov 24;270(47):28188-92

Sprenger H, Lloyd AR, Kelvin DJ. Promoter analysis of the human interleukin-8 receptor genes, IL-8RA and IL-8RB. Immunobiology. 1995 Jul;193(2-4):334-40

Strieter RM, Polverini PJ, Arenberg DA, Walz A, Opdenakker G, Van Damme J, Kunkel SL. Role of C-X-C chemokines as regulators of angiogenesis in lung cancer. J Leukoc Biol. 1995 May;57(5):752-62

Jones SA, Wolf M, Qin S, Mackay CR, Baggiolini M. Different functions for the interleukin 8 receptors (IL-8R) of human neutrophil leukocytes: NADPH oxidase and phospholipase D are activated through IL-8R1 but not IL-8R2. Proc Natl Acad Sci U S A. 1996 Jun 25;93(13):6682-6

Laudanna C, Campbell JJ, Butcher EC. Role of Rho in chemoattractant-activated leukocyte adhesion through integrins. Science. 1996 Feb 16;271(5251):981-3

Miller LJ, Kurtzman SH, Wang Y, Anderson KH, Lindquist RR, Kreutzer DL. Expression of interleukin-8 receptors on tumor cells and vascular endothelial cells in human breast cancer tissue. Anticancer Res. 1998 Jan-Feb;18(1A):77-81

Wilkinson NC, Navarro J. PU.1 regulates the CXCR1 promoter. J Biol Chem. 1999 Jan 1;274(1):438-43

Godaly G, Bergsten G, Hang L, Fischer H, Frendéus B, Lundstedt AC, Samuelsson M, Samuelsson P, Svanborg C.

Neutrophil recruitment, chemokine receptors, and resistance to mucosal infection. J Leukoc Biol. 2001 Jun;69(6):899-906

Horikawa T, Kaizaki Y, Kato H, Furukawa M, Yoshizaki T. Expression of interleukin-8 receptor A predicts poor outcome in patients with nasopharyngeal carcinoma. Laryngoscope. 2005 Jan;115(1):62-7

Liu Y, Yang S, Lin AA, Cavalli-Sforza LL, Su B. Molecular evolution of CXCR1, a G protein-coupled receptor involved in signal transduction of neutrophils. J Mol Evol. 2005 Nov;61(5):691-6

Murphy C, McGurk M, Pettigrew J, Santinelli A, Mazzucchelli R, Johnston PG, Montironi R, Waugh DJ. Nonapical and cytoplasmic expression of interleukin-8, CXCR1, and CXCR2 correlates with cell proliferation and microvessel density in prostate cancer. Clin Cancer Res. 2005 Jun 1;11(11):4117-27

Pignatti P, Moscato G, Casarini S, Delmastro M, Poppa M, Brunetti G, Pisati P, Balbi B. Downmodulation of CXCL8/IL-8 receptors on neutrophils after recruitment in the airways. J Allergy Clin Immunol. 2005 Jan;115(1):88-94

Stemmler S, Arinir U, Klein W, Rohde G, Hoffjan S, Wirkus N, Reinitz-Rademacher K, Bufe A, Schultze-Werninghaus G, Epplen JT. Association of interleukin-8 receptor alpha polymorphisms with chronic obstructive pulmonary disease and asthma. Genes Immun. 2005 May;6(3):225-30

Lundstedt AC, McCarthy S, Gustafsson MC, Godaly G, Jodal U, Karpman D, Leijonhufvud I, Lindén C, Martinell J, Ragnarsdottir B, Samuelsson M, Truedsson L, Andersson B, Svanborg C. A genetic basis of susceptibility to acute pyelonephritis. PLoS One. 2007 Sep 5;2(9):e825

Maxwell PJ, Gallagher R, Seaton A, Wilson C, Scullin P, Pettigrew J, Stratford IJ, Williams KJ, Johnston PG, Waugh DJ. HIF-1 and NF-kappaB-mediated upregulation of CXCR1 and CXCR2 expression promotes cell survival in hypoxic prostate cancer cells. Oncogene. 2007 Nov 15;26(52):7333-45

Abolhassani M, Aloulou N, Chaumette MT, Aparicio T, Martin-Garcia N, Mansour H, Le Gouvello S, Delchier JC, Sobhani I. Leptin receptor-related immune response in colorectal tumors: the role of colonocytes and interleukin-8. Cancer Res. 2008 Nov 15;68(22):9423-32

Shamaladevi N, Lyn DA, Escudero DO, Lokeshwar BL. CXC receptor-1 silencing inhibits androgen-independent prostate cancer. Cancer Res. 2009 Nov 1;69(21):8265-74

Singh S, Nannuru KC, Sadanandam A, Varney ML, Singh RK. CXCR1 and CXCR2 enhances human melanoma tumourigenesis, growth and invasion. Br J Cancer. 2009 May 19;100(10):1638-46

Eikawa S, Ohue Y, Kitaoka K, Aji T, Uenaka A, Oka M, Nakayama E. Enrichment of Foxp3+ CD4 regulatory T cells in migrated T cells to IL-6- and IL-8-expressing tumors through predominant induction of CXCR1 by IL-6. J Immunol. 2010 Dec 1;185(11):6734-40

Varney ML, Singh S, Li A, Mayer-Ezell R, Bond R, Singh RK. Small molecule antagonists for CXCR2 and CXCR1 inhibit human colon cancer liver metastases. Cancer Lett. 2011 Jan 28;300(2):180-8

Liu X, Peng J, Sun W, Yang S, Deng G, Li F, Cheng JW, Gordon JR. G31P, an antagonist against CXC chemokine receptors 1 and 2, inhibits growth of human prostate cancer cells in nude mice. Tohoku J Exp Med. 2012;228(2):147-56

Sapoznik S, Ortenberg R, Galore-Haskel G, Kozlovski S, Levy D, Avivi C, Barshack I, Cohen CJ, Besser MJ, Schachter J, Markel G. CXCR1 as a novel target for directing reactive T cells toward melanoma: implications for adoptive cell transfer immunotherapy. Cancer Immunol Immunother. 2012 Oct;61(10):1833-47

Bondurant KL, Lundgreen A, Herrick JS, Kadlubar S, Wolff RK, Slattery ML. Interleukin genes and associations with colon and rectal cancer risk and overall survival. Int J Cancer. 2013 Feb 15;132(4):905-15

Singh JK, Farnie G, Bundred NJ, Simões BM, Shergill A, Landberg G, Howell SJ, Clarke RB. Targeting CXCR1/2 significantly reduces breast cancer stem cell activity and increases the efficacy of inhibiting HER2 via HER2-dependent and -independent mechanisms. Clin Cancer Res. 2013 Feb 1;19(3):643-56

This article should be referenced as such:

Sapoznik S, Kozlovski S, Markel G. CXCR1 (chemokine (C-X-C motif) receptor 1). Atlas Genet Cytogenet Oncol Haematol. 2014; 18(1):8-11.