Atlas of Genetics and Cytogenetics in Oncology and Haematology

OPEN ACCESS JOURNAL AT INIST-CNRS

Gene Section
Mini Review

CCR2 (chemokine (C-C motif) receptor 2)

Jérôme Moreaux

Institut de Recherche en Biotherapie, INSERM U847, Hopital Saint-Eloi, CHU de Montpellier, 80 av Augustin Fliche, 34295 Montpellier Cedex 5, France (JM)

Published in Atlas Database: May 2011

Online updated version : http://AtlasGeneticsOncology.org/Genes/CCR2ID964ch3p21.html
DOI: 10.4267/2042/46068

Identity

Other names: CC-CKR-2; CCR2A; CCR2B; CD192; CKR2; CKR2A; CKR2B; CMKBR2; FLJ78302; MCP-1-R; MGC103828; MGC111760; MGC168006

HGNC (Hugo): CCR2

Location: 3p21.31

DNA/RNA

Note

CCR2 is a member of the beta chemokine receptor family. CCR2 is a seven transmembrane protein similar to G protein-coupled receptors. This gene encodes two isoforms of a receptor for monocyte chemoattractant protein-1, a chemokine which specifically mediates monocyte chemotaxis. Monocyte chemoattractant protein-1 is involved in monocyte infiltration in inflammatory diseases such as rheumatoid arthritis as well as in the inflammatory response against tumors. The receptors encoded by this gene mediate agonist-dependent calcium mobilization and inhibition of adenylyl cyclase. This gene is located in the chemokine receptor gene cluster region including CCR1, CCRL2, CCR3, CCR5 and CCXCR1 on chromosome 3p.

Description

Size: 7195 bases.
2 isoforms:

- C-C chemokine receptor type 2 isoform A. CCDS43078.1
- C-C chemokine receptor type 2 isoform B. CCDS46813.1

Transcription

Homo sapiens chemokine (C-C motif) receptor 2 (CCR2), transcript variant A, mRNA: 2689 bp.
Homo sapiens chemokine (C-C motif) receptor 2 (CCR2), transcript variant B, mRNA: 2335 bp.

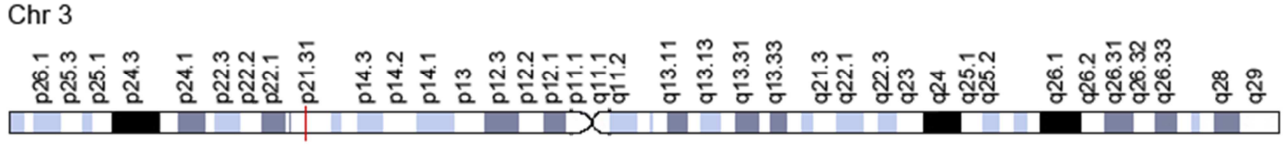
Pseudogene

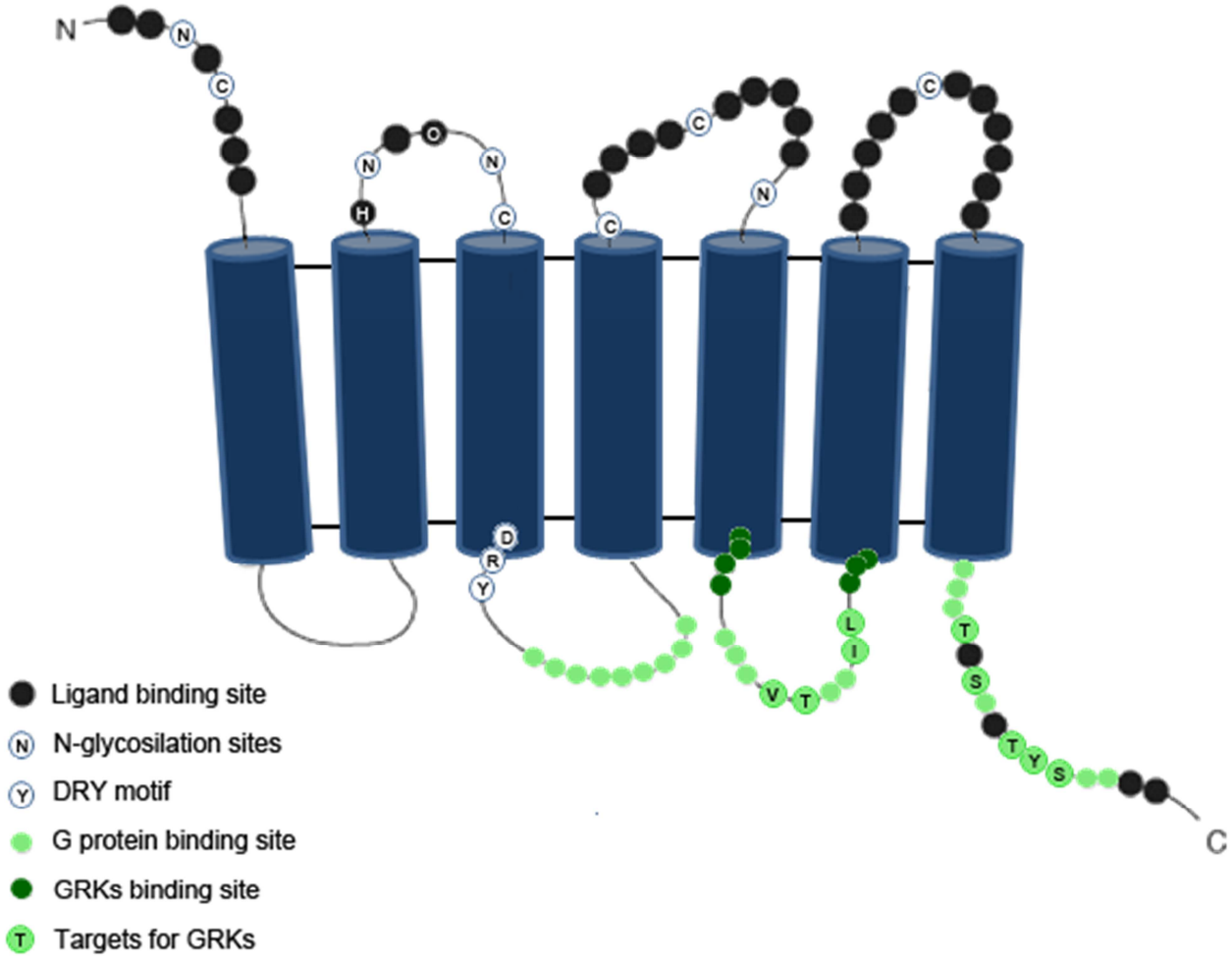
No pseudogenes have been reported for CCR2.

Protein

Note

Chemokine receptors are cytokine receptors found on the surface of cells, which interact with a type of cytokine called a chemokine. They have a 7 transmembrane structure and couple to G-protein for signal transduction within a cell, making them members of a large protein family of G protein-coupled receptors. Following interaction with their specific chemokine ligands, chemokine receptors trigger a flux in intracellular calcium (Ca^{2+}) ions (calcium signaling). This causes cell responses, including the onset of a process known as chemotaxis that traffics the cell to a desired location within the organism.





Structure of CCR2. The typical serpentine structure is depicted with three extracellular (top) and three intracellular (bottom) loops and seven transmembrane domains.

Chemokine receptors share many common structural features; they are composed of about 350 amino acids that are divided into a short and acidic N-terminal end, seven helical transmembrane domains with three intracellular and three extracellular hydrophilic loops, and an intracellular C-terminus containing serine and threonine residues that act as phosphorylation sites during receptor regulation. The first two extracellular loops of chemokine receptors are linked together by disulfide bonding between two conserved cysteine residues. The N-terminal end of a chemokine receptor binds to chemokine(s) and is important for ligand specificity. G-proteins couple to the C-terminal end, which is important for receptor signaling following ligand binding.

Description

374 amino acids; 41915 Da.

Expression

Peripheral blood monocytes, activated T cells, B cells and immature dendritic cells.

Localisation

Cell membrane; multi-pass membrane protein.

Function

Receptor for the MCP-1/CCL2, MCP-3/CCL7 and MCP-4/CCL13 chemokines. Transduces a signal by increasing the intracellular calcium ions level. Alternative coreceptor with CD4 for HIV-1 infection.

Homology

CCR2 proteins contains amino acid sequence homology to other C-C chemokines. CCR1 (56%), CCR5 (71%), CCR3 (78%), CCR4 (75%).

Implicated in

Multiple myeloma

Prognosis

In a cohort of 80 patients with Multiple Myeloma (MM), patients with active disease showed significant lower expression of CCR1, CCR2 and CXCR4 than patients with non-active disease.

Oncogenesis

CCR1 and CCR2 are overexpressed in myeloma cells compared to normal B cells. Osteoclasts express genes coding for CCR2 chemokines specifically (CCL2, CCL7, CCL8, and CCL13) and high CCR2 gene expression in myeloma cells is associated with increased bone lesions in MM patients. CCR2 is significantly overexpressed in MM cells compared to normal bone marrow plasma cells. Osteoclasts can directly recruit MMC by CCR2 chemokines production, promote MMC survival, growth, and drug resistance by producing various growth factors. MMC will promote osteoclast progenitor recruitment and differentiation producing CCL3, MIP-1beta, and CXCL12 chemokines, IGF-1, and increasing RANKL production by stromal cells. Osteoclasts are the main cells in the BM environment that produce various CCR2 chemokines enabling malignant plasma cells attraction.

Neuroblastoma

Oncogenesis

98 untreated primary neuroblastomas from patients with metastatic disease were analyzed for tumor-infiltrating iNKTs (Valpha24-Jalpha18-invariant natural killer T cells) using RT-PCR and immunofluorescent microscopy. 53% of tumors contained iNKTs. CCR2 is more frequently expressed by iNKT compared to T cells and natural killer cells from blood. iNKTs migrate toward neuroblastoma cells in a CCL2-dependent manner, preferentially infiltrating MYCN nonamplified proto-oncogene tumors that express CCL2.

Melanoma

Oncogenesis

MCP-1 may play a role in tumor angiogenesis and early tumor growth of human malignant melanoma by inducing VEGF and inflammatory cytokines production (IL-1alpha and TNFalpha by the tumor-associated macrophages (TAM) and autocrine/paracrine effects on melanoma cells in a mouse model.

Prostate cancer

Prognosis

The pleiotropic roles of CCL2 in the development of prostate cancer are mediated through its receptor, CCR2. An association between prostate cancer progression and CCR2 expression was demonstrated on tissue microarray specimens of patients. CCR2 mRNA and protein were significantly overexpressed within prostate cancer metastatic tissues compared to localized prostate cancer and benign prostate tissue. CCR2 overexpression was also associated with higher Gleason score and higher clinical pathologic stages.

Oncogenesis

CCL2 support prostate cancer cell survival via PI3K/AKT in vitro. CCL2 derived from human bone marrow endothelial cells induces PC-3 cell line transendothelial cell migration via activation of the small GTPase Rac. In a cell co-culture system, prostate cancer cell-conditioned medium induces CCL2 overexpression in endothelial cells and osteoblasts. In osteoblasts, this secretion is mediated in part by parathyroid hormone-related protein.

In mouse model, neutralizing antibody against CCL2 inhibits prostate cancer PC-3 and VCaP growth in bone. Same results were obtained with CCL2 knockdown. CCL2 induces surviving expression in prostate cancer cells and protect them from autophagic death.

Breast cancer

Prognosis

Overexpression of the chemokine CCL2 is frequently associated with advanced tumor stage and metastatic relapse in breast cancer.

Oncogenesis

Overexpression of CCL2 promotes breast cancer metastasis to both lung and bone in mice. Blocking CCL2 with a neutralizing antibody reduced lung and bone metastases. The enhancement of lung metastases by CCL2 was associated with increased macrophage infiltration. In bone, it was associated with osteoclast differentiation. CCL2 produced by breast tumor cells activates CCR2 positive stromal cells of monocytic origin (including macrophages and preosteoclasts) leading to metastases in lung and bone.

Esophageal carcinoma

Oncogenesis

CCL2 is expressed by tumor cells of esophageal squamous cell carcinoma. CCL2 produced by tumor cell and CCR2 expressed on vascular endothelial cells may participate in esophageal carcinoma tumor angiogenesis.

Gastric cancer

Oncogenesis

CCL2 produced by human gastric carcinoma cells is involved in angiogenesis via macrophage recruitment and activation via CCR2. CCL2 produced by gastric carcinoma cells induces tumor growth in ectopic xenografts and increased tumorigenicity and induced lymph node metastases and ascites in orthotopic xenografts.

References

De Vos J, Couderc G, Tarte K, Jourdan M, Requirand G, Delteil MC, Rossi JF, Mechti N, Klein B. Identifying intercellular signaling genes expressed in malignant plasma cells by using complementary DNA arrays. Blood. 2001 Aug 1;98(3):771-80

Ohta M, Kitadai Y, Tanaka S, Yoshihara M, Yasui W, Mukaida N, Haruma K, Chayama K. Monocyte chemoattractant protein-1 expression correlates with macrophage infiltration and tumor vascularity in human gastric carcinomas. Int J Oncol. 2003 Apr;22(4):773-8

Koide N, Nishio A, Sato T, Sugiyama A, Miyagawa S. Significance of macrophage chemoattractant protein-1 expression and macrophage infiltration in squamous cell carcinoma of the esophagus. Am J Gastroenterol. 2004 Sep;99(9):1667-74

Metelitsa LS, Wu HW, Wang H, Yang Y, Warsi Z, Asgharzadeh S, Groshen S, Wilson SB, Seeger RC. Natural killer T cells infiltrate neuroblastomas expressing the chemokine CCL2. J Exp Med. 2004 May 3;199(9):1213-21

Kuroda T, Kitadai Y, Tanaka S, Yang X, Mukaida N, Yoshihara M, Chayama K. Monocyte chemoattractant protein-1 transfection induces angiogenesis and tumorigenesis of gastric carcinoma in nude mice via macrophage recruitment. Clin Cancer Res. 2005 Nov 1;11(21):7629-36

Vande Broek I, Leleu X, Schots R, Facon T, Vanderkerken K, Van Camp B, Van Riet I. Clinical significance of chemokine receptor (CCR1, CCR2 and CXCR4) expression in human myeloma cells: the association with disease activity and survival. Haematologica. 2006 Feb;91(2):200-6

Chavey C, Bibeau F, Gourgou-Bourgade S, Burlinchon S, Boissière F, Laune D, Roques S, Lazennec G. Oestrogen receptor negative breast cancers exhibit high cytokine content. Breast Cancer Res. 2007;9(1):R15

Koga M, Kai H, Egami K, Murohara T, Ikeda A, Yasuoka S, Egashira K, Matsuishi T, Kai M, Kataoka Y, Kuwano M, Imaizumi T. Mutant MCP-1 therapy inhibits tumor angiogenesis and growth of malignant melanoma in mice. Biochem Biophys Res Commun. 2008 Jan 11;365(2):279-84

Soria G, Ben-Baruch A. The inflammatory chemokines CCL2 and CCL5 in breast cancer. Cancer Lett. 2008 Aug 28;267(2):271-85

Lu X, Kang Y. Chemokine (C-C motif) ligand 2 engages CCR2+ stromal cells of monocytic origin to promote breast cancer metastasis to lung and bone. J Biol Chem. 2009 Oct 16;284(42):29087-96

Zhang J, Lu Y, Pienta KJ. Multiple roles of chemokine (C-C motif) ligand 2 in promoting prostate cancer growth. J Natl Cancer Inst. 2010 Apr 21;102(8):522-8

Zhang J, Patel L, Pienta KJ. CC chemokine ligand 2 (CCL2) promotes prostate cancer tumorigenesis and metastasis. Cytokine Growth Factor Rev. 2010 Feb;21(1):41-8

Moreaux J, Hose D, Kassambara A, Reme T, Moine P, Requirand G, Goldschmidt H, Klein B. Osteoclast-gene expression profiling reveals osteoclast-derived CCR2 chemokines promoting myeloma cell migration. Blood. 2011 Jan 27;117(4):1280-90

This article should be referenced as such:

Moreaux J. CCR2 (chemokine (C-C motif) receptor 2). Atlas Genet Cytogenet Oncol Haematol. 2011; 15(11):938-941.