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Gene Section
Mini Review

CXCR3 (chemokine (C-X-C motif) receptor 3)

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Identity

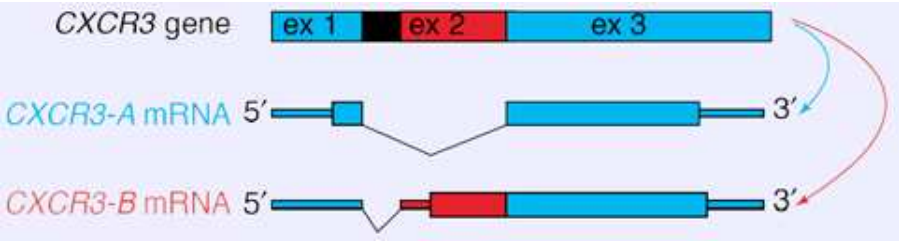
Other names: CD182; CD183; CKR-L2; CMKAR3; CXC-R3; CXCR-3; GPR9; IP10; IP10-R; Mig-R; MigR
HGNC (Hugo): CXCR3
Location: Xq13.1
Note: CXCR3 is a G protein-coupled receptor with selectivity for three chemokines, termed IP10 (CXCL10), Mig (CXCL9) and I-TAC (CXCL11). IP10, Mig and I-TAC belong to the structural subfamily of CXC chemokines, in which a single amino acid residue separates the first two of four highly conserved Cys residues. Binding of chemo-kines to CXCR3 induces cellular responses that are involved in leukocyte traffic, most notably integrin activation, cytoskeletal changes and chemotactic migration. A hallmark of CXCR3 is its prominent expression in in vitro cultured effector/memory T cells, and in T cells present in many types of inflamed tissues. In addition, IP10, Mig and I-TAC are commonly produced by local cells in inflame-matory lesions, suggesting that CXCR3 and its chemokines participate in the recruitment of infla-mematory cells.

DNA/RNA

Note
CXCR3-A is a receptor for CXCL9, CXCL10 and CXCL11 and mediates the proliferation of human mesangial cells. CXCR3-B is a receptor for CXCL4 and also mediates the inhibitory activities of CXCL9, CXCL10 and CXCL11 on the growth of human microvascular endothelial cells. CXCR3-B may play a role in angiogenesis.

Description

Alternative splicing of the CXCR3 gene generates two distinct chemokine receptors. The CXCR3 gene generates two distinct mRNAs, resulting from alternative splicing of three different exons. The already known CXCR3, renamed CXCR3-A,results from splicing of a single intron. The first exon encodes 4 amino acids and the second exon encodes the remaining 312 amino acids. The recently identified splicing variant, CXCR3-B,results from an alternative splicing between the same donor site used by the known CXCR3-A and a novel acceptor site localized 233 base pairs upstream of the CXCR3-A acceptor site. This novel exon (exon2) encodes 51 different amino acids, which are selectively expressed in CXCR3-B.



The CXCR3 gene generates two distinct mRNAs.

Transcription

CXCR3-A and CXCR3-B transcripts of 1.6 and 1.8 kb, respectively.

Protein

Description

Size: 368 amino acids; 40660 Da.

Expression

CXCR3-A and CXCR3-B are mainly expressed in the heart, kidney, liver and skeletal muscle. CXCR3-A is also expressed in the placenta.

Localisation

Cell membrane; Multi-pass membrane protein.

Function

Dijkstra et al. showed that human CCL21, in the absence of its primary receptor, CCR7, is a functional ligand for CXCR3, inducing chemotaxis in adult microglial cells, but not in kidney epithelial cells. CCL21 signaling through CXCR3 depends on the cellular background in which CXCR3 is expressed.
Lasagni et al. found that both CXCR3-A and CXCR3-B bound CXCL9, CXCL10, and CXCL11, but only CXCR3-B bound CXCL4 (PF4), following expression in a microvascular endothelial cell line. Overexpression of CXCR3-A induced an increase in endothelial cell survival, whereas overexpression of CXCR3-B upregulated apoptotic pathways. CXCR3B-specific monoclonal antibodies reacted with neoplastic tissue endothelial cells, providing evidence that CXCR3-B is expressed in vivo and may account for the angiostatic effects of CXC chemokines.

Implicated in

Melanoma

Prognosis

Forty primary melanomas were analyzed. 57% of the tumors expressed CXCR3 and 35% expressed CXCR4 on the melanoma cells. Co-expression of both CXCR3 and CXCR4 conferred a significantly poorer outcome similar to the expression of CXCR4 alone.

Oncogenesis

Several human melanoma cell lines as well as melanoma cells on macroscopically infiltrated lymph nodes express the chemokine receptors CXCR3 and CXCR4. In a murine model with B16F10 melanoma cells, reduced CXCR3 expression by antisense RNA showed significantly reduced metastatic activities to lymph nodes.

Breast cancer

Oncogenesis

Activation of Ras in MDA-MB-435 and MCF-7 breast cancer cells promotes CXCL10 expression and down-regulates CXCR3-B expression to promote tumor cell proliferation. In a murine model of metastatic breast cancer, a small molecular weight antagonist of CXCR3 inhibits lung metastasis.

Colon cancer

Prognosis

In 92 colon cancer samples, 31 samples (33.7%) expressed CXCR3 on cancer epithelial cells. The patients with CXCR3-positive tumors had a significantly poorer prognosis than those with CXCR3-negative tumors. In addition, the patients with tumors dobly positive for CXCR3 and CXCR4 had a significantly poorer prognosis than those with tumors positive only for CXCR4 or doubly negative.

Oncogenesis

In a murine model of metastatic colon cancer, overexpression of CXCR3 significantly promotes lymph node metastasis, although metastasis to the liver or lung was unaffected.

Renal cell carcinoma

Oncogenesis

Real-time RT-PCR analysis showed that expression levels of I-TAC, Mig, and CXCR3 in RCC tissues were greater 14.9 times, 30.3 times, and 9.9 times, respectively, compared with the levels in the corresponding normal kidney tissues.

B-cell Lymphoma

Oncogenesis

CXCR3 expression was seen in 37 of 39 cases of chronic lymphocytic leukemia / small lymphocytic lymphoma, whereas mantle cell lymphoma (30 cases), follicular lymphoma (27 cases) and small noncleaved cell lymphoma (8 cases) were negative in all but 2 cases.

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