CXCL5 (chemokine (C-X-C motif) ligand 5)

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Identity

Other names: ENA-78, SCYB5

HGNC (Hugo): CXCL5

Location: 4q13.3

Local order: On the reverse strand.

DNA/RNA

Description

The CXCL5 gene is located on human chromosome 4 at 4q13.3, starting at position 74861359 and ending at position 74864496 on the reverse strand. It consists of 4 exons.

Transcription

The transcript consists of 2538bp. The coding sequence begins at residue 119 and ends at residue 463. The mRNA is polyadenylated and is translated to produce a 114 residue polypeptide.

Protein

Description

The full length polypeptide consists of 114 amino acids. The N-terminal 36 amino acids are removed to generate the mature molecule 78 amino acids in length. An E-L-R (Glu-Leu-Arg) motif, important for receptor binding, is found immediately N-terminal to the C-X-C motif (Cys-Val-Cys). The E-L-R motif is found in pro-angiogenic chemokines (Belperio et al., 2000), while the presence of the C-X-C motif places this protein into the CXC-chemokine family. CXCL5 has homology to CXCL8 (Walz et al., 1991).

Expression

Ubiquitous in adult.

Localisation

Secreted.

Function

Chemotaxis, neutrophil activation, angiogenesis. Human CXCL5 is a substrate for several proteases (Van den Steen et al., 2003; Dean et al., 2008; Starr et al., 2012). These include matrix metalloprotease MMP-1, MMP-9, MMP-12, and MMP-25 (MT6-MMP), which cleave the N-terminal region of the mature (78aa) polypeptide.
MMP-12 has been reported to inactivate CXCL5, as it results in cleavage within the ELR motif, as well as between residues 5 and 6. MMP-25 is also thought to activate CXCL5 by removing the N-terminal 7 amino acids from the mature polypeptide, resulting in a 71 amino acid product (8-78). MMP-9 digests CXCL5 at multiple sites: early proteolysis involves the N-terminal region and is thought to potentiate CXCL5 activity, whereas later proteolysis (upon extended incubation with the protease) results in CXCL5 inactivation.

**Homology**

IL-8. Conservation of this gene is observed in chimpanzee, dog and cow.

**Implicated in**

*Cancer, pulmonary fibrosis, inflammatory diseases and endometriosis*

**Note**

CXCL5 is reportedly overexpressed in a number of human tumors such as head and neck squamous cell carcinoma, gastric, pancreatic, colorectal, prostate and lung cancer as well as in lung tissue of patients with pulmonary fibrosis. CXCL5 was found to be upregulated in many types of inflammatory conditions. It plays a significant role in inflammation that occurs in diseases such as acute coronary syndrome, allergy, rheumatoid arthritis, inflammatory bowel disease, pulmonary sarcoidosis, pancreatitis and endometriosis.

**Oncogenesis**

Abnormal expression of CXCL5 has been correlated with increased tumor cell motility and proliferation in vitro and increased tumorigenicity in vivo. It is also associated with worse clinical prognosis in several cancer types.

**Head and neck squamous cell carcinoma**

**Oncogenesis**

It has been reported that metastatic head and neck cancer cells express comparatively high levels of CXCL5 relative to primary tumor cells, as measured by microarray and confirmed by quantitative real-time PCR and analysis of conditioned medium (Miyazaki et al., 2006). Biological consequences of CXCL5 overexpression have been investigated in terms of tumor cell proliferation and motility, both of which are reduced if CXCL5 expression is inhibited. In vivo growth of xenografted tumor cells was abrogated when CXCL5 expression was repressed by small hairpin RNA.

**Gastric cancer**

**Oncogenesis**

Overexpression of CXCL5 has been found to correlate with late stage gastric cancer and high N stage, suggesting a role for CXCL5 in progression of gastric cancer and nodal metastasis (Park et al., 2007). This was revealed by immunostaining of gastric tumors for CXCL5, as well as enzyme-linked immunosorbent assay (ELISA) measurement of serum CXCL5 levels.

**Colorectal cancer**

**Oncogenesis**

Low expression of CXCL5 in a rat model of colorectal cancer has been reported to increase the tumorigenic potential of cells that would otherwise form a less aggressive type of colon cancer (Speetjens et al., 2008). It has also been observed that human patients with low CXCL5 levels in their colorectal tumors had a poorer prognosis than those with higher expression of CXCL5.

**Pancreatic cancer**

**Oncogenesis**

CXCL5 is secreted by pancreatic cancer cell lines, and antibody-mediated blockade of the CXCR2 receptor inhibits neovascularization in corneal angiogenesis assays (Wente et al., 2006). CXCL5 is also overexpressed in pancreatic cancer specimens, and is linked to poor patient survival (Frick et al., 2008). Blocking CXCR2 with an antibody, or inhibiting CXCL5 expression with siRNA, inhibits tumor xenograft formation. CXCL5 activates signaling through AKT-, ERK- and STAT-dependent pathways in pancreatic cancer cells (Li et al., 2011).
Prostate cancer
Oncogenesis
Androgen-independent prostate cancers tend to overexpress CXCL5. It has been reported that CXCL5 overexpression leads to increased cell migration and epithelial-to-mesenchymal transition (Kuo et al., 2011).

Non-small cell lung cancer
Oncogenesis
CXCL5 was found to play a role in development of non-small cell lung cancer by enhancing tumor angiogenesis (Arenberg et al., 1998). High expression of CXCL5 was correlated with vascularity of tumors. Passive immunity against CXCL5 resulted in a reduction of tumor growth, vascularity and metastases in vivo, although there was no effect of passive immunity on tumor cell proliferation.

Pulmonary fibrosis
Note
Analysis of bronchoalveolar lavage (BAL) fluid and lung tissue from patients with idiopathic pulmonary fibrosis revealed elevated levels of the angiogenic chemokines CXCL5 and CXCL8, together with a relative decrease of angiostatic factors, correlating with increased fibrosis of lung tissue (Streiter et al., 2007).

Acute coronary syndrome (ACS)
Note
Examination of CXCL5 in inflammation associated with acute coronary syndrome indicated that a polymorphism in CXCL5 (156G>C; rs352046) was linked to a 2.7-fold rise in 3-year mortality (all causes; C/C genotype only). Mortality was reduced in G/G genotype individuals by the use of statins. Treatment of human umbilical vein endothelial cells (HUVECs) with atorvastatin in vitro reduced the levels of IL-1β-induced CXCL5 in a dose-dependent manner (Zineh et al., 2008).

Allergy
Note
Activated mast cells have been shown to increase CXCL5 production significantly compared to the level of CXCL5 in resting cells. Supernatants from sonicated MC-9 mast cells elicited a significant influx of neutrophils when injected intratracheally in mice. When the same supernatants were preincubated with CXCL5-specific antibodies, neutrophil influx was dramatically reduced, implicating CXCL5 produced by activated mast cells as a critical chemoattractant for neutrophils (Lukacs et al., 1998).

Rheumatoid arthritis (RA)
Note
CXCL5 is reported to be significantly elevated in synovial fluid of patients with rheumatoid arthritis compared to patients with other forms of arthritis (Koch et al., 1994). Studies of rat adjuvant-induced arthritis (AIA), as a model for RA, showed elevated CXCL5 levels in serum with progressive development of arthritis compared to control animals. Joint homogenates also had increased levels of CXCL5 and this correlated with disease progression. Anti-CXCL5 antibody treatments prior to the onset of AIA decreased the severity of the disease (Halloran et al., 1999). The results indicate that CXCL5 plays an important role in the onset and progression of RA.

Inflammatory bowel disease
Note
Immunohistochemical studies of colonic epithelial cells in normal subjects and patients with inflammatory bowel disease showed that CXCL5 is expressed predominantly by crypt epithelial cells (Keates et al., 1997). CXCL5 production is significantly higher in patients with ulcerative colitis, with less intense expression in Crohn's disease patients.

Pulmonary sarcoidosis
Note
Increased levels of CXCL5 were found in the serum and BAL fluid of patients with pulmonary sarcoidosis compared to normal subjects, as judged by ELISA. BAL levels of CXCL5 were elevated in stage III sarcoidosis (Sujiyama et al., 2006).

Pancreatitis
Note
Patients with severe acute pancreatitis had significantly higher serum levels of CXCL5 compared to individuals with mild acute pancreatitis (Shokuhi et al., 2002). Samples from patients with chronic pancreatitis also showed higher expression of CXCL5 than normal pancreatic tissues, predominantly in centroacinar ducts of pancreatic lobuli (Saurer et al., 2000). These findings suggest a role for CXCL5 in development and maintenance of both acute and chronic pancreatitis.

Endometriosis
Note
CXCL5 has also been implicated in the pathogenesis of endometriosis, with elevated levels of CXCL5 found in peritoneal fluid of patients with endometriosis compared to control subjects (Mueller et al., 2003). Further studies showed that glandular cells, stromal fibroblasts and peritoneal macrophages were primarily responsible for CXCL5 production in patients with endometriosis. Elevated levels of CXCL5 have also been found in the follicular fluid of patients with endometriosis compared to controls (Wunder et al., 2006). Together, these studies implicate CXCL5 in the pathogenesis of endometriosis.
References


