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Gene Section
Review

CX3CL1 (chemokine (C-X3-C motif) ligand 1)

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Abstract

Review on CX3CL1, with data on DNA/RNA, on the protein encoded and where the gene is implicated.

Identity

Other names: ABCD-3, C3Xkine, CXC3, CXC3C, NTN, NTT, SCYD1, fractalkine, neurotactin

HGNC (Hugo): CX3CL1

Location: 16q21

DNA/RNA

Note

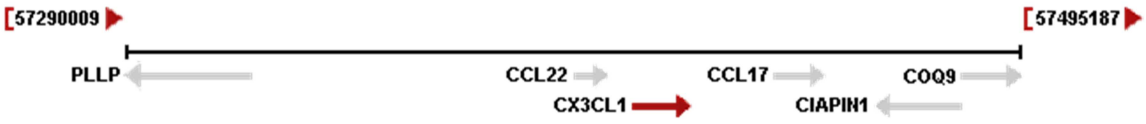
CX3CL1 gene is located on the long arm of chromosome 16 at position 13 and contains three exons. This gene encodes for a protein of 397 aa. The first 24 aa represents the peptide signal.

Transcription

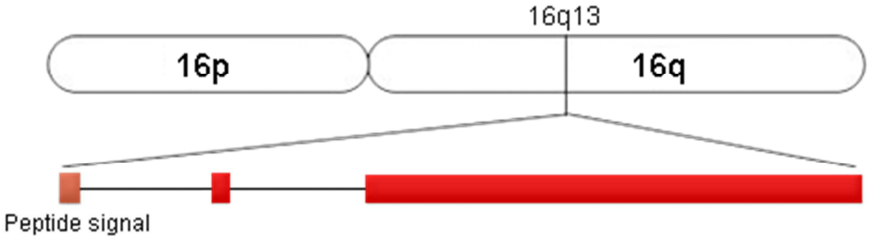
Only one type of transcript has been described.
The 1194-nucleotide transcript encodes a protein of 397 amino acid residues.
The primary structure of human CX3CL1 consists of an N-terminal 24-amino acid signal sequence followed by the chemokine domain of CX3CL1, a mucin-like stalk, a transmembrane domain and an intracellular part.

Pseudogene

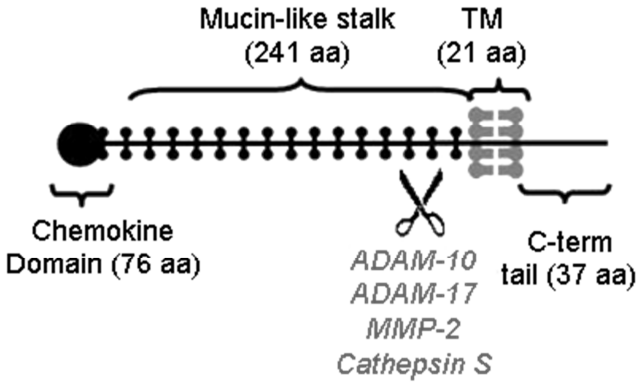
None described so far.



Chromosome 16; NC_000016.9.



The CX3CL1 gene comprises 3 exons. The first codes for the peptide signal.



Secondary structure of the membrane form of CX3CL1 (Bazan et al., 1997; Fong et al., 2000).

Protein

Description

CX3CL1 is synthesized as a membrane protein consisting of the chemokine domain, a highly glycosylated mucin-like stalk, a transmembrane domain and an intracellular part. Cleavage by some metalloproteinases like ADAM-10 (Hundhausen et al., 2003), ADAM-17 (Garton et al., 2001; Tsou et al., 2001), MMP-2 (Bourd-Boittin et al., 2009) and cathepsin-S (Clark et al., 2009) gives raise to the soluble form of CX3CL1 consisting of the chemokine domain and the glycosylated mucin-like stalk (Bazan et al., 1997; Schulte et al., 2007). The C-terminal part contains two putative adaptor protein-2 (AP-2)-binding motifs, that control the constitutive endocytosis of the whole protein (Huang et al., 2009) mediated by clathrin and dynamin-1 (Robinson et al., 2002).

Expression

The chemokine CX3CL1 is constituvely expressed in microglial cells (Cross and Woodroofe, 1999), astrocytes (Hatori et al., 2002) and some neurons (Harrison et al., 1998; Cross and Woodroofe, 1999; Maciejewski-Lenoir et al., 1999; Deiva et al., 2004). Its expression is stimulated by inflammatory ligands in vascular endothelial cells (Fong et al., 1998; Imaizumi et al., 2000; Fraticelli et al., 2001; Schäfer et al., 2007), renal endothelial (Cross and Woodroofe, 1999) and epithelial cells (Chakravorty et al., 2002), in aortic (Ludwig et al., 2002; Ollivier et al., 2003) and pulmonary (Sukkar et al., 2004) smooth muscle cells and in dendritic cells (Papadopoulos et al., 1999; Dichmann et al., 2001; Pallandre et al., 2008).

Localisation

The chemokine CX3CL1 is mainly localized at the plasma membrane (Bazan et al., 1997; Fong et al., 2000). Its biosynthesis in the Golgi and/or ER organelles starts as an non glycosylated and intracellular.

Function

The function of CX3CL1 relies on both of its forms: the soluble form, released by metalloproteinases, is chemoattractant while the membrane form mediates stable adhesion of leukocytes such as integrins (Fong et al., 1998; Haskell et al., 1999).

Implicated in

Glioblastoma

Note

Both CX3CL1 and CX3CR1 are expressed in human surgical glioma samples. The expression of CX3CL1 was inversely correlated with patient overall survival (Erreni et al., 2010). The presence of the rare variant CX3CR1 was shown to be associate with a longer mean survival (Rodero et al., 2008).

Atherosclerosis

Note

The CX3CL1 molecule, with its unique CX3CR1 receptor (Imai et al., 1997), has been shown to be central in cellular processes leading to atherosclerosis. In animal models, the deletion of CX3CR1 genes lead to decreased disease (Combadière et al., 2003; Lesnik et al., 2003). In human, the presence of the rare variant CX3CR1 I249 is an independent genetic risk factor for coronary artery disease (Moatti et al., 2001).

Neurotoxicity

Note

By binding to its receptor CX3CR1, the CX3CL1 molecule decreases the microglial neurotoxicity mediated by inflammatory molecules (reactive species, matrix metalloproteinase, inflammatory cytokines) (Cardona et al., 2006). CX3CL1 acts by binding to CX3CR1 present on microglia to modulate microglial activation (Cho et al., 2011). However converse data also exist. During focal cerebral ischemia, elimination of CX3CL1

signaling was associated with smaller infarct and enhanced recovery (Dénes et al., 2008).

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