Gene Section
Review

CSF1R (colony stimulating factor 1 receptor, formerly McDonough feline sarcoma viral (v-fms) oncogene homolog)

John Adams Fischer, Stefano Rossetti, Nicoletta Sacchi

Roswell Park Cancer Institute, Department of Cancer Biology, Elm and Carlton Streets, Buffalo, NY 14263, USA (JAF, SR, NS)

Published in Atlas Database: April 2008

Online updated version: http://AtlasGeneticsOncology.org/Genes/CSF1RID40161ch5q32.html

DOI: 10.4267/2042/44403

This work is licensed under a Creative Commons Attribution-Noncommercial-No Derivative Works 2.0 France Licence.

© 2009 Atlas of Genetics and Cytogenetics in Oncology and Haematology

Identity

Other names: C-FMS; CD115; CSF-1-R; CSFR; EC 2.7.10.1; FIM2; FMS; c-fms
HGNC (Hugo): CSF1R
Location: 5q32

Local order: The human CSF1R gene is located at the distal end of the q arm of chromosome 5 with telomere to centromere orientation. Proximal flanking genes include CSF2 (GM-CSF) and IL-3 at 5q31.1. Distal flanking genes include PDGFRB at 5q31-q32.

Note

CSF1R (C-FMS) is the human cellular homologue of the retroviral oncogene v-fms. The v-fms oncogene, first identified and isolated by Heisterkamp et al. in 1983, is transduced by the feline sarcoma virus Susan McDonough (SM) and HZ-5 strains, which cause fibrosarcomas in domestic cats. The v-fms oncogene is equivalent to the c-fms gene in its sequence, but has undergone genetic alterations, which constitutively activate the receptor kinase in the absence of its ligand, the colony stimulating factor-1 (CSF1). Infection of mammalian cells with v-fms leads to cell transformation in vitro and in vivo.

DNA/RNA

Note

The presence of an anti-sense CSF1R transcript starting within the FIRE region has been reported in mouse macrophages and B cells.

Description

The human CSF1R gene, on the minus strand, spans a region of 60,077 bases (Start: 149,413,051 bp from pter; End: 149,473,128 bp from pter) interrupted by introns ranging from 26kb for intron 1, to a range between 6.3kb to less than 0.1 kb for the other introns. The human CSF1R gene is composed of a total of 22 exons, of which the first exon is non-coding and where the remaining 21 exons (starting with exon 2) encode for the CSF1R protein.

The human CSF1R and mouse Csf1r genomic structures are highly conserved.

Transcription

The 5' end of the human CSF1R gene has 2 alternative transcription start site regions, preceded by two alternative promoters. The transcription of CSF1R mRNA can be initiated at the two independent start sites in a tissue specific manner. The transcription of exon 1 through exon 22 occurs only in placental trophoblasts, and is driven by a trophoblast-specific promoter approximately 20kb upstream of the first exon. The transcript produced is predicted to be approximately 4kb long. In macrophages and a few other tissues (see expression section) transcription of CSF1R occurs only from exon 2 through exon 22 producing a transcript predicted to be approximately 3.9kb in length, which is translated into the CSF1R protein.
The transcription this transcript is under the control of two major regulatory regions, which are highly conserved between human and mouse: the Promoter upstream of exon 2 and the fms-intronic regulatory region (FIRE). Most studies on CSF1R transcriptional regulation have focused on the mouse gene. However, most of the features of mouse Csf1r are highly conserved in human.

The mouse Csf1r promoter is TATA-less, and drives transcription from multiple sites (known as broad class transcription start sites). This promoter is not GC rich and there are no CpG islands in the vicinity. This promoter contains binding sites for various transcription factors including: PU.1, C/EBP, PAX5, and FUS/TLS-TBP. The mouse FIRE region is located in the second intron, approximately 2kb downstream from the transcription start site. It contains binding sites for a number of transcription factors including: Sp1 / C/EBP. With a few exceptions, the features described for the mouse Csfr1 regulatory regions are highly conserved in human. Specifically, the human CSF1R can be regulated in a hormone dependent fashion via a glucocorticoid response element present in the human CSF1R promoter, but not in the mouse Csf1r promoter.

**Pseudogene**

The first CSF1R intron contains a transcriptionally inactive ribosomal protein L7 processed pseudo-gene that is oriented in the opposite direction of the CSF1R gene itself. This pseudogene is not functional but its sequence is highly conserved across all mammalian species.

**Protein**

**Description**

The CSF1R protein consists of 972 amino acids and has a molecular mass of approximately 108 kDa. However due to post-translational modifications,
CSF1R Protein Structure. A. Schematic representation of CSF1R protein showing the CSF1-binding IG domains in the extracellular portion, and the tyrosine kinase catalytic domain in the intracellular portion. Phosphorylated tyrosines (Y) are indicated.

which include phosphorylation, glycosylation, and the acquisition of N-linked oligosaccharides, the proteins molecular size increases.

The CSF1R protein also contains a signal peptide and a 512 amino acid N-terminal extracellular segment which contains the ligand binding domain, a hydrophobic 25 amino acid membrane spanning region, and intracellular domain 435 amino acids in length that includes all sequences necessary for tyrosine kinase activity (occurring at tyrosine (Y) Y699 and Y708, as well as Y809). The CSF1R protein contains a glycine-rich signature sequence that is characteristic of kinases, as well as an ATP binding site at lysine (K) K616. The immature intracellular glycoprotein has a molecular mass of 130 kDa after it acquires N-linked oligosaccharides of the high mannose type during co-translational glycosylation. The molecular mass of CSF1R is increased further during intracellular transport to the plasma membrane, where the glycoprotein's N-linked carbohydrates undergo modifications in the Golgi complex, resulting in an increase to 150 kDa molecular mass. There are variations in molecular mass of CSF1R across species due to the differential processing of carbohydrate chains in a species-specific manner.

**Expression**

The major site of CSF1R expression is in macrophages. In hematopoiesis, CSF1R is upregulated during monocytic differentiation, but is downregulated during granulopoiesis. CSF1R is expressed predominantly in committed macrophage precursors (CFU-Ms), monocytes, and tissue macrophages. CSF1R mRNA can be detected granulocytes, but is not translated. CSF1R mRNA/protein expression has been reported also in non-hematopoietic cells such as trophoblasts (where it is seen to derive from an alternative transcript including the non-coding exon 1), osteoclasts, smooth muscle cells, and neurons, as well as in female mammary gland epithelium during development and lactation. Expression of CSF1R mRNA/protein has also been reported in breast, ovarian, and endometrial tumors, as well as in hepatocellular carcinomas. CSF1R expression during hematopoiesis is regulated by tissue-specific sets of transcription factors that play a key role in myeloid differentiation. CSF1R is activated in a synergistic manner by the co-expression of the macrophage-specific transcription factor Pu.1 and c-Ets-2. During B-cell lineage restriction and differentiation, the CSF1R gene is repressed by the transcription factor PAX5. It has been shown that PAX5 is required during B-cell differentiation to keep CSF1R in a silent state. It has also been shown that CSF1R can be repressed by Foxp1, a forkhead transcription factor that is in turn regulated by the Beta-2-integrin Mac-1.

CSF1R Protein Structure. B. Diagram of the 2.7 A Crystal Structure of the Autoinhibited Human CSF1R/kinase Domain (as described in Walter et al. J. Mol. Biol. 2007).
Localisation
CSF1R is located at the cell plasma membrane. Transport of CSF1R from the endoplasmic reticulum (the site of synthesis) to the plasma membrane occurs efficiently with detection of the receptor at the surface within 30 minutes of synthesis.

Function
CSF1R is the receptor for the ligand colony stimulating factor-1 (CSF1). CSF1R is an integral transmembrane glycoprotein that exhibits ligand-induced tyrosine-specific protein kinase activity, which triggers a signaling cascade eventually affecting transcription of CSF1-responsive genes. CSF1R tyrosine phosphorylation is induced upon binding of CSF1, leading to activation of Ras / Erk and class I-A phosphatidylinositol 3-kinase signaling pathways, which in turn activate the signal transducers and activators of transcription (STATs) pathways, specifically STAT1, STAT3, and STAT5. CSF1R activation by CSF1 results in increased growth, proliferation and differentiation.

Homology
Like the CSF1R gene, the CSF1R protein sequence appears to be conserved across Euteleostomi (vertebrates) including: Homo sapiens (Human), Canis lupus familiaris (Dog), Mus musculus (Mouse), Rattus norvegicus (Rat), Gallus gallus (Chicken), and Danio rerio (Zebrafish). CSF1R is a member of the gp140 family of the type I cytokine receptor group and shares a high degree of amino acid sequence homology to platelet-derived growth factor receptor (PDGFRB), specifically in its kinase domain.

Mutations
Germinal
None identified as of yet.

Somatic
Chromosomal abnormalities: A partial deletion of chromosome 5 containing the CSF1R locus has been consistently observed in patients with myelodysplastic syndrome. The CSF1R locus is also affected by the acute megakaryoblastic leukemia-associated translocation t(3;5)(p21;q33) in which the CSF1R gene on chromosome 5 is fused to the RBM6 gene on chromosome 3, resulting in a fusion protein RBM6-CSF1R.

Gene mutations: CSF1R point mutations have been detected mainly in hematopoietic/lymphoid tissue and liver, where they correlate with myelodysplastic syndrome and acute myeloid leukemia (AML) and hepatocellular carcinoma, respectively. Specifically, mutations at codons 301 (exon 7) and 969 (exon 22) seem to occur with a higher frequency in both tissues. According to earlier studies these are activating mutations that would play a role in leukemogenesis.

However, later studies have failed to find these mutations in AML patients. Additional mutations were discovered in AML patients at codons 245 (exon 6) and 413 (exon 9). However, their contribution to leukemogenesis is not known. Epi-mutations: Specific fusion proteins resulting from leukemia-associated chromosomal translocations, including the AML1-MTG fusion proteins, result in transcriptional downregulation of specific AML1 target genes such as CSF1R. AML1-MTG-induced CSF1R downregulation is epigenetic, as it is marked by specific repressive histone changes as well as DNA hypermethylation at the CSF1R regulatory regions. CSF1R epigenetic down-regulation is associated with block of myeloid differentiation and defects in cell proliferation in vitro.

Implicated in
Myelodysplastic syndrome (MDS)
Disease
The human CSF1R gene is consistently lost by partial deletions occurring in chromosome 5 in MDS patients. Moreover, specific deletion of the CSFS1R gene has been detected in as many as 40% of MDS patients.

Acute Myeloid Leukemia (AML)
Disease
Early studies had suggested a link between AML and the presence of CSF1R codon 301 and 969 activating mutations. While there is strong evidence that these mutations have potential transforming activity, recent studies have failed to find these mutations in AML patients. Thus the pathogenic role of CSF1R mutations in leukemogenesis is still controversial. CSF1R might be involved in leukemia through mechanisms other than gene mutations. CSF1R downregulation has been reported in specific AML subtypes. One of the factors that may lead to CSF1R downregulation is the expression of the AML-associated fusion proteins AML1-MTG8 (AML1-ETO) and AML1-MTG16, derived from the t(8;21) and t(16;21) chromosomal translocations, respectively. Specifically, in patients with the t(8;21) translocation, which accounts for approximately 12% of all AML cases, CSF1R down-regulation is marked by epigenetic repressive changes (epi-mutations).

t(3;5)(p21;q33) in Acute Megakaryoblastic Leukemia (AMKL)
Disease
CSF1R has been reported to be affected by the chromosomal translocation t(3;5)(p21;q33) in the AMKL cell line MKP1. The fusion protein produced by this translocation, RBM6-CSF1R is found only in the cytoplasm and is constitutively active in the megakaryocyte lineage. The RBM6-CSF1R confers IL-3 independence to the mouse Pro-B cell line BaF3, and induced myeloproliferative disease in a murine transplant model. The AMKL subtype represents 1% or
less of the cases of AML. It most often occurs in children, and is associated with Down syndrome. The prognosis for AMKL is poor.

**Breast Cancer**

**Disease**

58% of all breast carcinomas and 85% of invasive breast carcinomas express higher levels of CSF1R compared to normal resting breast tissue. It has been demonstrated that exogenous expression of CSF1R in untransformed human mammary epithelial cells results in aberrant acinar morpho-genesis, anchorage-independent growth and an invasive phenotype. Expression of CSF1R in breast tumors correlates with increased invasiveness and adverse prognostic features like high histological grade, and an advanced clinical stage of presentation of breast cancer.

**Cervical Cancer**

**Disease**

A significant increase in CSF1R expression has been reported in cervical carcinomas as compared to normal cervical tissue. The expression of CSF1R in cervical cancer is usually associated with a more aggressive and invasive disease. It has been suggested that there is an autocrine mode of regulation by CSF1 in this cancer cell type.

**Breakpoints**

**Note**

The only breakpoint known for the CSF1R gene can be inferred by the identification of the novel fusion protein RBM6-CSF1R, in which the N-terminal portion of the RBM6 (a.a. 1-36) is fused to the C-terminal portion of CSF1R (a.a. 574-972). This fusion protein is predicted to be produced by the translocation t(3;5)(p21;q33).

**References**


Roussel MF, Dull TJ, Rettenmier CW, Ralph P, Ullrich A, Sherr CJ. Transforming potential of the c-fms proto-oncogene (CSF-1 receptor). Nature. 1987 Feb 5-11;325(6104):549-52

Sherr CJ. The role of the CSF-1 receptor gene (C-fms) in cell transformation. Leukemia. 1988 Dec;2(12 Suppl):132S-142S


Zent CS, Mathieu C, Claxton DF, Zhang DE, Tenen DG, Rowley JD, Nucifora G. The chimeric genes AML1/MDS1 and AML1/EAP inhibit AML1B activation at the CSF1R promoter, but only AML1/MDS1 has tumor-promoter properties. Proc Natl Acad Sci U S A. 1996 Feb 6;93(3):1044-8


Wang Y, Berezovska O, Fedoroff S. Expression of colony stimulating factor-1 receptor (CSF-1R) by CNS neurons in mice. J Neurosci Res. 1999 Sep 1;57(5):616-32

