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Gene Section
Short Communication

SOCS6 (suppressor of cytokine signaling 6)

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Abstract

The suppressor of cytokine signaling (SOCS) family of proteins are well known negative regulators of cytokine receptors signaling consisting of eight structurally similar proteins, SOCS1-7 and CIS. A key feature of this family of proteins is the presence of two structural motifs: a centrally located SH2 domain and a SOCS box in the C-terminus. The SOCS box mediates the interaction with the Elongins B and C complex while an additional motif mediates its interaction with Cullin 5 to assemble a Cullin/Ring ubiquitin ligase. In this complex SOCS6 acts as a substrate recognition subunit through interactions mediated by the N-terminus and the SH2 domain. SOCS6 interacts with tyrosine kinase receptors FLT3 and c-KIT and modulate their ubiquitination and function.

Keywords
CIS4; SSI4; CIS-4; SOCS4; STAI4; SOCS-4; SOCS-6; STATI4; HSPC060.

Identity

Other names: CIS-4, CIS4, HSPC060, SOCS-4, SOCS-6, SOCS4, SSI4, STAI4, STATI4

HGNC (Hugo): SOCS6

Location: 18q22.2

DNA/RNA

Description

According to Entrez-Gene SOCS6 maps to NC_000018.10 in the region between 70288901 and 70330199 on the plus strand. According to UCSC genome browser SOCS6 has two exons, one shorter of 190 base pairs and other on of 5656 base pairs.

Transcription

SOCS6 mRNA has 5864 nucleotides (NM_004232.3). The open reading frame (ORF) includes 1608 nucleotides situated in exon 2 (Figure 1). Transcription is induced by activation of certain cytokine receptors and growth factor receptors.

Pseudogene

Chromosome 11q14.1 has a SOCS6 pseudogene in between 83789973 and 83791578 spanning 1606 base pairs. The pseudogene has a 92% sequence similarity with the SOCS6 gene.

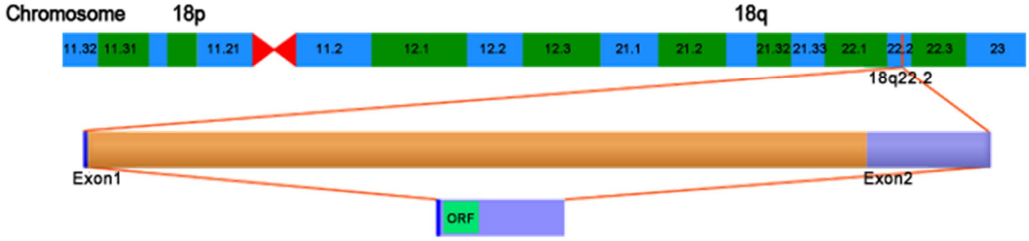

Figure 1: SOCS6 mapped on Human Dec. 2013 (GRCh38/hg38) assembly in chromosome 18: (70288901-70330198) spanning 41298 base pairs using UCSC Genome Browser.

Figure 2: Domain structure of SOCS6 protein, SB stand for SOCS-box.

Protein

Description

SOCS6 gene is expressed as an approximately 60 kDa protein with calculated isoelectric point 6.83 and total charge -0.76 at pH 7.

SOCS6 has a still uncharacterized long N-terminal region, an SH2 domain and a C-terminal SOCS-box (Figure 2).

The protein is mainly expressed in the cytosol and associates with multiple proteins (Bayle et al., 2004; Bayle et al., 2006; Hwang et al., 2007; Kazi et al., 2012; Zadjali et al., 2011).

Most relevant for SOCS6 function is its capacity to associate with Elongin B and Elongin C and with Cullin 5 to assemble a functional E3 ubiquitin ligase complex.

Expression

SOCS6 is highly to moderately expressed in heart, parathyroid, salivary gland, stomach, thyroid, kidney and skeletal muscle tissues. Expression was also reported in mature hematopoietic cells and melanocyte.

Localisation

SOCS6 predominantly localizes to the cytosol and nucleus (Hwang et al., 2007). The N-terminal amino acids 1-210 influence its nuclear localization. Additionally SOCS6 localizes to the mitochondria and probably to the inner-surface of cell membrane (Lin et al., 2013).

Function

SOCS6 is involved in protein destabilization and to some extent acts as a signaling molecule. The presence of multiple domains in SOCS6 protein facilitates interaction with multiple signaling molecules. The SOCS6 SH2 domain associates with specific tyrosine phosphorylated proteins and the SOCS-box recruits the ubiquitin machinery directing proteins for degradation (Kazi et al., 2014; Zadjali et al., 2011).

Homology

Homologous proteins are found in various species including monkey, mouse, rat, frog and zebra fish etc. Monkey SOCS6 displays as high as 98% sequence similarity to human SOCS6, while zebra fish SOCS6 display 68% sequence similarity. In any case, the SOCS-box sequence is highly conserved and maintains a 100% sequence similarity.

Mutations

Note

In the COSMIC database 52 different SOCS6 mutations have been listed, where 40 mutations are non-synonymous (figure 3), two mutations introduce stop codons at 199 and 328 sites, one mutation is reported as a 254A and 255G deletion and the other 9 mutations are synonymous mutations.

Implicated in

Hepatocellular carcinoma

Note

SOCS6 expression is significantly reduced in hepatocellular carcinoma and lower SOCS6 correlates with overall and disease free survival (Qiu et al., 2013).

Lung squamous cell carcinoma

Note

Loss of SOCS6 function is associated with poor prognosis in primary lung squamous cell carcinoma. Copy number loss and slight hyper-methylation that was correlated with disease progression was reported in this disease (Sriram et al., 2012).

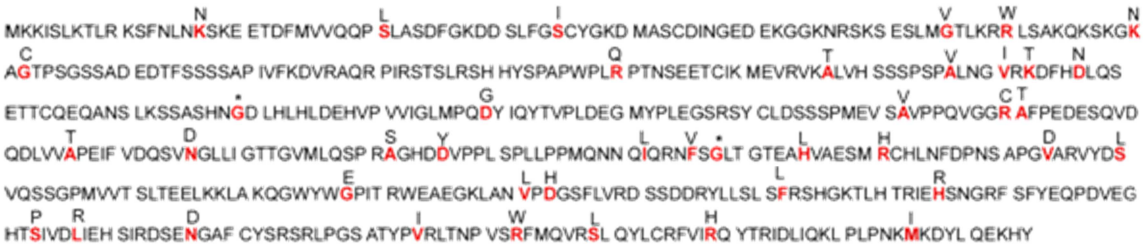

Figure 3: Mutations in SOCS6 protein according to COSMIC database.

Prostate cancer

Note

The down-regulation of SOCS6 has been reported in prostate cancer tissues with a higher Gleason score, the advanced pathological stage, positive metastasis, and the positive PSA failure suggesting that SOCS6 might be associated with aggressive progression of prostate cancer (Zhu et al., 2013).

Gastric cancer

Note

Loss of SOCS6 function has been reported in gastric cancer. Allelic loss and promoter hyper-methylation occur in this cancer. Ectopic expression of SOCS6 led to reduced cell growth and colony formation of gastric cancer cell (Lai et al., 2010).

Pancreatic cancer

Note

The microRNA miR-424-5p is a suppressor of SOCS6 expression. This microRNA is up-regulated in pancreatic cancer resulting in down-regulation of SOCS6 (Wu et al., 2013). Down-regulation of SOCS6 led to increased proliferation, migration and invasion of pancreatic cancer cells suggesting SOCS6 acts as a tumor suppressor in pancreatic cancer.

Glucose metabolism

Note

SOCS6 has been shown to interact with the insulin receptor (INSR), INSR substrates IRS2 and IRS4, and negatively regulates insulin signaling (Krebs et al., 2002; Mooney et al., 2001). Although these findings suggest that SOCS6 might play a role in glucose metabolism, mice lacking SOCS6 gene did not display any significant defects in glucose metabolism apart from a slight growth retardation (Krebs et al., 2002).

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