

Gene Section

Review

SOCS2 (suppressor of cytokine signaling 2)

Indranil Paul, Leandro Fernández-Pérez, Amilcar Flores-Morales

Institut for Veteriaer Sygdomsbiologi, Danish Cancer Society Research Center, University of Copenhagen, Denmark (IP, AFM); University of Las Palmas de GC, Faculty of Health Sciences, Molecular and Translational Endocrinology Group, c/ Dr. Pasteur s/n - Campus San Cristobal, 35016 - Las Palmas, Spain, (LFP)

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Abstract

Review on SOCS2, with data on DNA, on the protein encoded, and where the gene is implicated.

Keywords: SOCS2; proteasome; immune cell differentiation; neuronal development; inflammation; cancer; diabetes

Identity

Other names: CIS-2, CIS2, Cish2, SOCS-2, SSI-2, SSI2, STATI2

HGNC (Hugo): SOCS2

Location: 12q21.3-q23 (Yandava et al., 1999). Plus strand.

DNA/RNA

Description

NCBI Reference Sequence: NC_000012.12; Coding positions from 93,966,674 to 93,968,952 (length: 2,279 bp). Mouse SOCS2 gene is composed of 3 exons and 2 introns (Metcalf et al., 2000). Human SOCS-2 comprises 3 exons spanning approximately 6,38 kb of genomic DNA.

Transcription

2888 bp mRNA. There are 6 transcript variants. Transcript variant 5 is the largest and is cited here. The variants differ in their 5' UTR. All variants encode the same protein.

Protein

Description

Reference sequence for SOCS2 protein: NP_001257399.1. SOCS2 contains 198 amino acid residues with a molecular weight of 22172 Da. SOCS2 belongs to the SOCS box family. SOCS2 contains a C terminal SOCS box (residue 151-197) for ElonginB,C/Cullin5/Rbx2 interaction. The unstructured N-terminal region (residue 1-47) and the SH2 domain (residue 48-156) is implicated in substrate interaction. The SH2 domain is known to interact with conserved phosphotyrosine residues on target proteins imparting substrate specificity to SOCS box proteins.

Expression

SOCS mRNA and protein levels are constitutively low in unstimulated cells, but their expression is rapidly induced upon cytokine stimulation, thereby creating a negative feedback loop. Although constitutively expressed SOCS2 mRNA has been detected in several tissues and cell types, its expression is, in general, induced by stimulation with different cytokines and hormones (Rico-Bautista et al., 2006). SOCS2 promoter analysis indicates the presence of AhR and STAT5 binding sites that confer responsiveness to dioxin (Boverhof et al., 2004) and GH (Vidal et al., 2006), respectively.

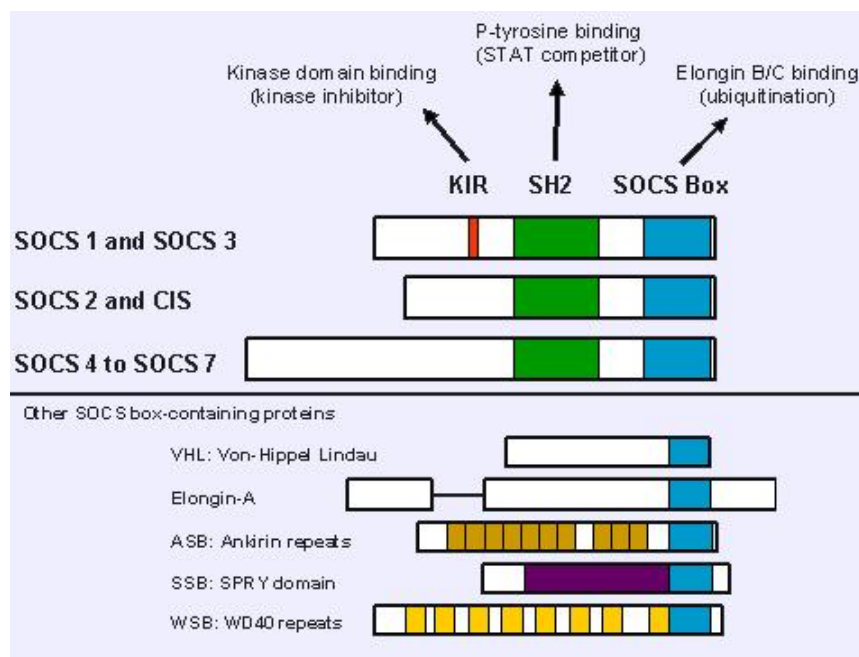


Diagram representing the structure of SOCS proteins. At least eight proteins belonging to the SOCS family of proteins are shown (upper panel). They are characterized by the presence of an SH2 central domain and the SOCS box domain at the C-terminus. A small domain called kinase inhibitory region (KIR), only found in SOCS1 and SOCS3, is shown as a small box at the N-terminal region. SOCS proteins can interact with phosphotyrosine phosphorylated proteins through their SH2 domain and with Elongin BC through their SOCS box domain. Other proteins containing a SOCS box domain but lacking a SH2 domain are also shown (lower panel). Adapted from Elliott and Johnston (Elliott and Johnston, 2004) with modifications.

Localisation

Intracellular, cytoplasm. SOCS2 can be located in the nuclear compartment when overexpressed in cell cultures.

Function

The function of SOCS proteins rely, on one hand, in their ability to bind tyrosine phosphorylated proteins through their SH2 domains and, on the other hand, to bind Elongins B/C through their SOCS box domains which in turn engages with the Cullin5/Rbx2 complex to assemble an E3 ubiquitin ligase.

SOCS family proteins form part of a classical negative feedback system that regulates cytokine signal transduction (Rico-Bautista et al., 2006).

Being a substrate recognition module for Cullin5/Rbx2 E3 ligase complex, SOCS2 is involved in regulating protein turnover by targeting proteins for proteasome-mediated degradation. SOCS2 binds and promote the ubiquitination of the Growth Hormone receptor (GHR) controlling GHR content in different tissues (Metcalf et al., 2000; Vesterlund et al., 2011).

Through the negative regulation of GHR signaling, SOCS2 exerts multiple actions in growth and metabolisms (Greenhalgh et al., 2005; Zadjali et al., 2012).

SOCS2 is also a critical regulator of inflammatory responses and immune cell differentiation (Machado et al., 2006; Hu et al., 2009a). Recently, SOCS2 is

being implicated in the progression of multiple human cancers (Schultheis et al., 2002; Harris et al., 2006; Newton et al., 2010; Iglesias-Gato et al., 2014).

Homology

HomoloGene (NCBI) Genes identified as putative homologs: NP_003868.1 SOCS2, H.sapiens; XP_001139989.1 SOCS2, P.troglodytes; XP_002798772.1 SOCS2, M.mulatta; XP_005629280.1 SOCS2, C.lupus; NP_803489.1 SOCS2, B.taurus; NP_001162126.1 Socs2, M.musculus; NP_478115.1 Socs2, R.norvegicus; NP_989871.1 SOCS2, G.gallus; NP_001120898.1 socs2, X.tropicalis; NP_001108022.1 socs2, D.rerio

Mutations

Note

There are 8 SNPs in coding regions of human SOCS2 which result in missense protein residues (NCBI dbSNP).

Homozygous null mice display gigantism (Metcalf et al., 2000), impaired innate immune cell differentiation and hypersensitivity to infections (Baetz et al., 2004; Yoshimura et al., 2005; Yoshimura et al., 2007). Homozygous null mice also display altered metabolic and inflammatory response to high fat feeding (Zadjali et al., 2012;). SNP: increasing the risk of type 2 diabetes (Kato et al., 2006)

Implicated in

Neural development

Note

SOCS2 plays a critical role in neuronal development, growth, and stem cell differentiation (Turnley et al., 2002).

Inflammation

Note

SOCS2 deficient dendritic cells and macrophages are hyper-responsive to microbial stimulation. SOCS2 deficient animals have uncontrolled production of inflammatory cytokines (IL-12, IFN γ and TNF α) and succumb to endotoxic shock, polymicrobial sepsis and other microbial infections (Esper et al., 2012).

SOCS2 plays a central role in differentiation and maturation of innate immune cells. Specifically, SOCS2 promotes generation of regulatory dendritic cells and macrophages (Novak et al., 1999; Jackson et al., 2004; Hu et al., 2012) and Treg population (Knosp et al., 2013).

Conversely, SOCS2 inhibits Th2 differentiation (Knosp et al., 2011).

Upon induced inflammatory challenge, absence of SOCS2 has been shown to render multiple immune cell types incapable of mounting anti-inflammatory responses.

Under resting conditions, SOCS2 null animals also display a population-bias towards a pro-inflammatory phenotype (Machado et al., 2006; Lee et al., 2010; Knosp et al., 2011; Posselt et al., 2011; Hu et al., 2012).

SOCS2 is known to inhibit TGF β , IL-4, IL-5, IL-10, IL-13 and IFN γ signaling (Knosp et al., 2011, Knosp et al., 2013).

In general, SOCS2 inhibits expression/secretion of pro-inflammatory cytokines and promotes generation of regulatory phenotype (anti-inflammatory) of immune cells. SOCS2 is thought to function in both MyD88 dependent and independent TLR4 signaling pathways because its downregulation negatively affects SAPK/JNK, p38 MAPK, ERK and NF κ B signaling (Hu et al., 2009b). Being an E3 ligase, SOCS2 regulates a number of proteins highly implicated in regulation of immune responses such as FoxP3 (Knosp et al., 2013) and TRAF6 (McBerry et al., 2012). SOCS2 also accelerates degradation of other members of the SOCS family such as SOCS1 and SOCS3 thus further impinging on downstream STAT signaling (Piessevaux et al., 2006; Tannahill et al., 2005). In turn, SOCS2 gene itself is under regulation of various inflammatory signals (e.g., LPS, dioxins, LipoxinA4) (Machado et al., 2006; Hu et al., 2009b, 2012) and cytokines (e.g., IL-4, IL-10, IFN β , IFN γ) (Knosp et al., 2011; Posselt et al., 2011).

Breast cancer

Note

SOCS2 expression inversely correlates with histological grades and is a positive prognostic factor (Farabegoli et al., 2005; Haffner et al., 2007). SOCS2 expression is induced by estrogen receptor (ER) activity. Estrogen treatment activates ER which in turn upregulates miR-191 which through downregulation of SATB1, a global chromatic remodeller, enhances SOCS2 transcription (Nagpal et al., 2013). Upregulation of SOCS2 upon estrogen administration antagonizes growth hormone action mediated through JAK2/STAT3 and STAT5 (Leung et al., 2003).

Colon cancer

Note

Both heterozygous and homozygous deletions of SOCS2 promoted spontaneous tumorigenesis in ApcMin/+ mice model of colorectal cancer. This is accompanied with a dramatic increase in AP-1 DNA binding (Newton et al., 2010). Acromegalic patients are prone to colonic polyp formation. These patients with hyperplastic polyps have increased SOCS2 transcripts (Bogazzi et al., 2009).

Myeloproliferative disorder

Note

SOCS2 gene is also hypermethylated in myeloproliferative disorders (Zhou et al., 2009; Zhang et al., 2013). SOCS2 is an important negative regulator of a constitutive active mutant of JAK2 (JAK2 V617F) (Etienne et al., 2007).

Prostate cancer

Note

SOCS2 is upregulated at both mRNA and protein levels in primary prostate cancer tissues relative to normal prostate. This upregulation is correlated to lower Gleason score, absence of metastasis and low PSA failure (Zhu et al., 2013). In contrast, SOCS2 expression is downregulated in castration resistant prostate cancer. This is partly explained by the fact that SOCS2 is transcriptionally upregulated by androgen receptor and inhibits GH signaling in prostate (Iglesias-Gato et al., 2014).

Other cancers

Note

SOCS2 gene is hypermethylated in melanoma and ovarian carcinoma (Marini et al., 2006; Liu et al., 2008). Lower SOCS2 expressions are also correlated to higher grades of hepatocellular carcinoma (Qiu et al., 2013).

Gigantism

Note

SOCS2 null mice are giants but not obese (Metcalf et al., 2000). SOCS2 deficient mice have growth and

metabolic characteristics that can be related to the enhanced GH actions (Rico-Bautista et al., 2005). On the other hand, the gigantic phenotype displayed by SOCS2 null mice is mechanistically different from that of human acromegalic patients as they do not exhibit increased circulating IGF-1 levels and seems to express reduced levels of GH (Greenhalgh 2005 and Zadjali 2012).

Disease

Gigantism is a condition characterized by excessive growth, significantly above average. This is caused due to an overactivation of growth hormone signaling.

Diabetes

Note

Genomic linkage analysis identified SOCS2 as a susceptibility gene for type 2 diabetes in a cohort of Japanese individuals. In the same study, adenovirus-mediated expression of the SOCS2 gene in MIN6 cells or isolated rat islets significantly suppressed glucose-stimulated insulin secretion (Kato et al., 2006). Constitutive SOCS2 expression in mice pancreatic beta cells interferes with proinsulin processing and leads to decreased insulin secretion (Lebrun et al., 2010). In contrast, SOCS2 null mice does not exhibit obvious defects in pancreatic beta cell function. When challenged with high fat diet SOCS2 null mice are protected from hepatic steatosis but exhibit an exacerbated inflammatory response and a worsening of insulin sensitivity as compared to wild-type mice on a similar diet.

Disease

Diabetes is a condition characterized by high blood sugar levels. This is caused due to inadequate insulin production or insulin resistance.

Osteoarthritis

Note

Analysis of SOCS2 null mice has revealed that the absence of SOCS2 induces a reduction in the trabecular and cortical volumetric bone mineral density (Lorentzon et al., 2005). SOCS2 induces the differentiation of C2C12 mesenchymal cells into myoblasts or osteoblasts (Ouyang et al., 2006).

Disease

Osteoarthritis is a condition characterized by mechanical degeneration of joints resulting in pain and restricted movement. This is caused due to hereditary and metabolic reasons.

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