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Gene Section
Review

PIAS1 (protein inhibitor of activated STAT, 1)

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Abstract

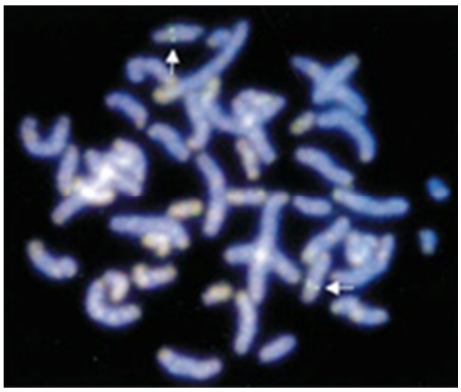
Review on PIAS1, with data on DNA/RNA, on the protein encoded and where the gene is implicated.

Identity

Other names: DDXBP1, GBP, GU/RH-II, ZMIZ3

HGNC (Hugo): PIAS1

Location: 15q23



Chromosomal mapping of PIAS1. Modified from Weiskirchen et al., 2001.

Note

PIAS1 gene was initially located at 15q22 (Weiskirchen et al., 2001).

DNA/RNA

Description

PIAS1 gene is composed of 14 exons and spans approximately 134,8 kb of genomic DNA.

Transcription

PIAS1 gene encodes a 2309 bp mRNA transcript.

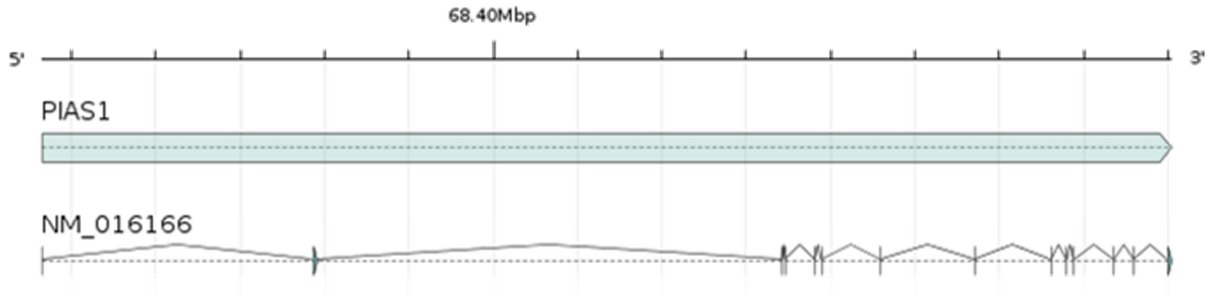
Pseudogene

No pseudogenes have been reported.

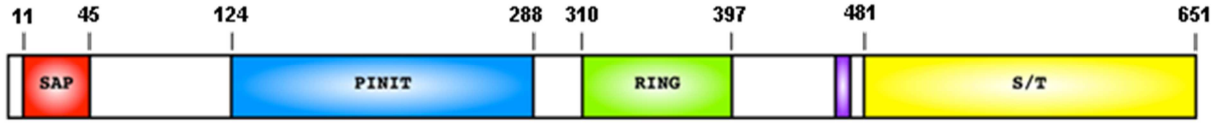
Protein

Description

The human PIAS1 protein is composed of 651 amino acids, with a predicted molecular weight of 71,85 kDa.
PIAS1 has five distinct functional domains, with different functions: the SAP (scaffold attachment factor-A/B, Acinus and PIAS), the PINIT motif, the RING-type zinc-binding domain, the SBD (SUMO binding domain, also indicated as SIM, SUMO interacting motif) and a C-terminal serine/threonine rich region.
The SAP domain contains a LXXLL motif which is involved in direct-DNA binding or in physical interaction with other proteins involved in DNA-binding, such as transcription factors, co-regulators and nuclear receptors (Aravind and Koonin, 2000).
The PINIT motif is involved in the sub-cellular organization of PIAS1 (Duval et al., 2003).
The RING domain is essential for the E3 SUMO-ligase activity of PIAS1 and also mediates protein-protein interactions (Hochstrasser, 2001).
The SBD domain interact in a non-covalently way with SUMO proteins (Rytinki et al., 2009).



Structural organization of PIAS1 human gene.



Schematic representation of PIAS1 protein. The different domains are illustrated. A purple square represents the SUMO binding domain (SBD).

The C-terminal portion of PIAS1 is a serine/threonine rich region: this is the most variable region within the PIAS proteins family. PIAS1 undergoes several post-translational modifications, including phosphorylation, acetylation, methylation, SUMOylation and ubiquitination (Liu et al., 2005; Depaux et al., 2007; Rytinki et al., 2009; Stehmeier and Muller, 2009; Weber et al., 2009).

Expression

PIAS1 is ubiquitously expressed.

Localisation

Nuclear.

Function

PIAS1 has been implicated in several cellular functions and most of them have been associated to its SUMO E3-ligase activity (Schimdt and Müller, 2003; Shuai and Liu, 2005; Rytinki et al., 2009).

Transcriptional regulation: PIAS1 is a negative regulator of several transcription factors. PIAS1 was initially described as a negative regulator of the STAT1 signal by blocking the DNA-binding activity of STAT1 (Liu et al., 1998). PIAS1 SUMOylates the TP53 tumor suppressor, inhibiting its activity (Kahyo et al., 2001; Schmidt and Müller, 2002). PIAS1 SUMOylates the androgen receptor (AR) repressing the AR-dependent transcription (Nishida and Yasuda, 2002). PIAS1 also regulates the homeoprotein Msx1 by regulating its subnuclear localization and its DNA-binding specificity in a SUMO E3-ligase independent manner (Lee et al., 2006). PIAS1 SUMOylates the progesterone receptor (PR), and cAMP attenuates ligand-dependent SUMOylation of PR (Jones et al., 2006).

Inflammation and immunity: upon various inflammatory stimuli, IKKa phosphorylates PIAS1 associating it with the promoter of NF-κB target genes (Liu et al., 2007).

PIAS1 regulates the natural T regulatory cells by restricting their differentiation through the recruitment of the protein DNA-methyltransferase and CBX5 at the FOXP3 promoter (Liu et al., 2010).

DNA damage: PIAS1 co-operates with PIAS4 promoting double-strand DNA breaks repair (Galanty et al., 2009).

Cancer: PIAS1 SUMOylates the promyelocytic leukemia (PML) gene and promotes its ubiquitin/proteasome-dependent degradation, inhibiting its tumor suppressor functions. PIAS1 also SUMOylates the PML-RARA oncoprotein of acute promyelocytic leukemia (APL); in this case, PIAS1-dependent SUMOylation is required for the degradation of PML-RARA in APL cells treated with arsenic trioxide (Rabellino et al., 2012).

Homology

PIAS1 belongs to the PIAS proteins family and is evolutionary conserved from yeast to man. PIAS1 can be found in Saccharomyces cerevisiae, in plants (Arabidopis thaliana and Oryza sativa), Caernorhabditis elegans, Drosophila melanogaster, Danio renio, Xenopus laevis, Gallus gallus and mammals. All PIAS1 orthologues share a high degree of homology.

The human PIAS family consists of at least 5 different members: PIAS1, PIAS2 (with two variants called PIASxα and PIASxβ), PIAS3 and PIAS4 (also known as PIASy). All family members share high protein homology, except for the C-terminus (Shuai and Liu, 2005; Rytinki et al., 2009).

Schematic representation of the mutations of human PIAS1 protein found in tumor samples. Notably, most of the mutations reside in the PINIT domain.

Mutations

Note

No translocations involving PIAS1 gene have been reported so far.

Germinal

No germinal mutations of PIAS1 have been reported.

Somatic

At least 25 different somatic mutations have been described in different tumor types. All the informations in this regard can be found at the COSMIC website.

Implicated in

Prostate cancer

Note

High expression of PIAS1 is found in malignant areas of prostate cancer as compared to benign areas. Immunohistochemistry staining positively correlates with positive staining for the PCNA and Ki-67 proliferative markers suggesting a pro-proliferative role of PIAS1 in prostate cancer (Hoefer, 2012).

Colon cancer

Note

Activated STAT3 signaling has been involved in colon cancer. PIAS1 is a negative regulator of the STAT signaling. Accordingly, PIAS1 expression is high in colonic non-tumor cells and adenomas, and lower in colon cancer cells (Coppola et al., 2009).

Gastric cancer

Prognosis

One study shows that 70% of the gastric tumors specimens analyzed show a low level of PIAS1 expression. Moreover, the low expression of PIAS1 significantly correlates with tumor staging (Chen et al., 2012).

Non-small cell lung cancer (NSCLC)

Note

PIAS1-dependent SUMOylation of PML leads to its degradation, blocking the tumor suppression activity of PML. Accordingly with this observation obtained with in vitro experiments, a correlation between high level of PIAS1 protein expression and low level of PML was reported in NSCLC specimens.

Furthermore, high expression of mRNA levels of PIAS1 in NSCLC specimens correlates with PIAS1 gene amplification (Rabellino et al., 2012).

Breakpoints

Note

None.

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