Atlas of Genetics and Cytogenetics in Oncology and Haematology

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Gene Section

Review

PIAS3 (protein inhibitor of activated STAT, 3)

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Identity

Other names: FLJ14651, KChAP, ZMIZ5
HGNC (Hugo): PIAS3
Location: 1q21.1

DNA/RNA

Note

The gene codes for a protein of the PIAS family (protein inhibitor of activated STAT (signal transducer and activator of transcription)). PIAS3 regulates the activity of several transcription factors by direct protein-protein interaction. Further, PIAS3 is a SUMO (small ubiquitin-like modifier)-E3 ligase, catalyzing the covalent, post-translational modification of specific target proteins with SUMO. Different splice variants of PIAS3 have been identified but the full-length sequence of some of these variants has not been described.

Description

The human PIAS3 gene is 10559 bp long and consists of 14 exons and 13 introns.

Transcription

Transcript length 2902 bp (CDS 1887 bp ; residues 628 aa).

Pseudogene

No pseudogene reported.

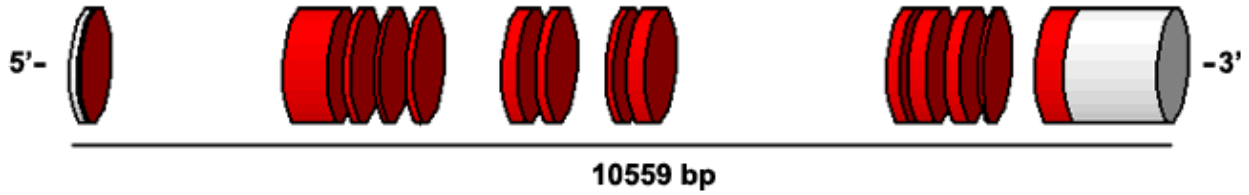

Figure 1. PIAS3 gene 10559 bp. Exons 1 to 14 (UTR in white, coding sequence in red) Exon 1: 1-115 (5'UTR: 1-91); Exon 2: 2075-2492; Exon 3: 2650-2734; Exon 4: 2963-3013; Exon 5: 3255-3345; Exon 6: 4201-4335; Exon 7: 4518-4623; Exon 8: 5195-5268; Exon 9: 5417-5577; Exon 10: 7928-8061; Exon 11: 8142-8310; Exon 12: 8495-8628; Exon 13: 8812-8849; Exon 14: 9369-10559 (3'UTR: 9636-10559).

Figure 2. The schematic domain structure of human PIAS3 protein is shown. SAP domain: nuclear localization and binding to DNA, transcription factors, coregulators. PINIT: nuclear retention, transcriptional repression. SP-RING: protein-protein interactions, interacts with the SUMO conjugase Ubc9, sumoylation. SIM: binding to SUMO. S/T: variable region, binding to coactivators.

Protein

Description

The human PIAS3 protein is a E3 SUMO-protein ligase consisting of 628 amino acids. It contains 5 conserved regions, the SAP, PINIT, SP-RING, SIM and S/T domains (figure 2).

Expression

PIAS3 is ubiquitously expressed.

Localisation

Nuclear as well as cytoplasmic localization.

Function

PIAS3 belongs to the mammalian protein inhibitor of activated STAT (PIAS) protein family, originally identified as cytokine-induced inhibitors of the STAT family of transcription factors. This protein class, referred to as SUMO-E3 ligases, increases the efficiency of SUMO conjugation. SUMO, a small ubiquitin-like modifier protein, is conjugated to a large number of cellular target proteins. Similar to enzymatic ubiquitination, the conjugation of specific SUMO proteins (SUMO-1-SUMO-3) to target proteins requires an E1-activating enzyme (Aos1/Uba2) as well as an E2-type SUMO-1-conjugating enzyme (Ubc9). Similar to many ubiquitin E3 ligases, these proteins contain a putative RING finger-like structure (SP-RING, figure 2), which is essential for their SUMO-E3 ligase activities toward various target proteins. Sumoylation is a dynamic process with highly diverse outcomes, ranging from changes in subcellular localization, signal transduction, transcriptional regulation to altered activity and stability of the modified protein. PIAS3 do, however, not only operate as SUMO-E3, since its coregulator effects are often independent of its RING-finger like domain but dependent on its capability to interact with sumoylated proteins via its conserved SIM (SUMO-interacting motif) or SAP (scaffold attachment factor-A/B/acinus/PIAS) domain (figure 2). Beside the N-terminal SAP, the SIM and the RING-type zinc-binding domain, a PINIT motif, and a serine/ threonine-rich C-terminal region (S/T) is conserved in PIAS3 (figure 2).
PIAS3 is involved in cytoplasmic regulation, such as functional interaction of PIAS3 with metabotropic glutamate receptor-8, voltage-gated potassium channel Kv1.5 and pyruvate kinase subtype M2, but the majority of so far reported interactions of the PIAS3 protein occurred with transcription factors or other proteins linked to nuclear regulation. PIAS3 can act in both transcriptional repression and activation. PIAS3 has been shown to repress STAT3 and Stat5 dependent transcriptional activation by blocking the DNA-binding of the factor without influencing its sumoylation. It interacts with and promotes sumoylation of the photoreceptor-specific transcription factor Nr2e3 when bound to specific promoters, which converts the factor to a transcriptional repressor. Moreover, PIAS3 was described as a repressor of microphthalmia transcription factor (MITF) and it was shown that PIAS3 blocks NF-kB mediated transcriptional activation by interacting with the p65/RelA subunit. Repression of IRF1-mediated transcription by PIAS3 has also been shown. PIAS3 has been shown to activate transcription mediated by Smad proteins through forming a complex with Smads and coactivator p300/CBP; moreover, PIAS proteins enhance steroid receptor-dependent transcription through an SP-RING-mediated interaction and sumoylation of the coactivator protein GRIP1/SCR2. Finally, PIAS3 was shown to modulate the ability of TIF2 to mediate ligand-enhanced transcription activation positively or negatively, for different steroid receptors.

Homology

The mammalian PIAS family consists of seven structurally related proteins (PIAS1, PIAS3, PIAS3b, PIASxa, PIASxb, PIASy, and PIASyE6) encoded by four genes. PIAS orthologs are found in nonvertebrate animal species, plants and yeasts.

Implicated in

Prostate Cancer

Oncogenesis

PIAS3 is expressed in normal prostate and in prostate cancer cells and has been shown to modulate the transcriptional activity of androgen receptor in prostate cancer cells. Moreover, PIAS3 (KChAP) induces increased K+ efflux and apoptosis in prostate cancer lines.

Glioblastoma multiforme (GBM)

Oncogenesis

The activation of STATs and loss of their natural inhibitors SOCS and PIAS is common in various human cancers. STAT3, a cytoplasmic transcription factor that becomes activated in response to a variety of cytokines and growth factors is aberrantly activated in GBM tumors. STAT3 activation correlates with strongly reduced PIAS3 protein expression in GBM tissues. Inhibition of PIAS3 resulted in enhanced glioblastoma cellular proliferation, and, conversely, PIAS3 overexpression inhibits STAT3 transcriptional activity, expression of STAT3-regulated genes, and cell proliferation. This suggests that the loss of PIAS3 in GBM contributes to enhanced STAT3 transcriptional activity and subsequent cell proliferation.

Melanoma

Oncogenesis

PIAS3 functions as a key molecule in suppressing the transcriptional activity of both MITF and STAT3, two transcription factors that play a major role in the development, proliferation and survival of mast cells

and melanocytes. In addition to its role in normal cell signaling, constitutively activated STAT3 signaling directly contributes to oncogenesis in many human cancers. STAT3 cooperates with MITF in the induction of cellular transformation. Evidence was provided suggesting that PIAS3 halt proliferation and induce apoptotic cell death in mast cells and in melanoma cells by inhibiting the transcriptional activity of the two oncogenic factors MITF and STAT3. Therefore PIAS3 may play a role in tumor suppression by inhibiting oncogenic processes induced by STAT3 and MITF.

Non-small cell lung cancer (NSCLC)

Disease

The Epidermal Growth Factor Receptor (EGFR)-STAT3 axis plays an important role in oncogenic signaling of non-small cell lung cancer (NSCLC). The negative regulator of STAT3-mediated transcriptional activation, PIAS3, was shown to modulate oncogenic EGFR-STAT3 signaling in lung cancer. Overexpression of PIAS3 decreases STAT3 transcriptional activity and proliferation of NSCLC cells and when used in conjunction with EGFR inhibitors, further increased the anti-proliferative effects. This suggests that PIAS3 acts as an inhibitor of EGFR-STAT3 induced oncogenic action.

To be noted

Note

TAR syndrome (Thrombocytopenia-absent radius) is a rare genetic disorder characterized by low platelet counts and bilateral radial aplasia. TAR is also frequently associated with cardiac abnormalities and cow's milk intolerance. In 2007 a research article described a common microdeletion of 200 kb on chromosome 1q21.1 in patients with TAR syndrome. PIAS3 is one of 11 genes encompassed by this microdeletion.

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