HIPK2 (homeodomain interacting protein kinase 2)

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Identity

Other names: DKFZp686K02111, FLJ23711, hHIPk2, PRO0593
HGNC (Hugo): HIPK2
Location: 7q34

DNA/RNA

Description
Zhang et al. (2005) reported 13 exons that span around 60 kb; however, up to 15 exons are listed in different databases.

Transcription
Around 15 kb mRNA (full-length); 3594 bp open reading frame.
At least two alternative transcripts.
Entrez Nucleotide:
[NM_022740.4] Homo sapiens HIPK2, transcript variant 1; 15245 bp linear mRNA; full-length isoform,
[NM_001113239.2] Homo sapiens HIPK2, transcript variant 2; 15164 bp linear mRNA; this variant lacks an internal segment in the CDS, the resulting isoform is shorter.
Uniprot/HB/Prot [Q9H2X6]:
[Q9H2X6-1] full-length isoform (1),
[Q9H2X6-2] isoform (2),
[Q9H2X6-3] isoform (3).
Ensemble Gene [ENSG00000064393]; 4 transcripts:
HIPK2-001 [ENST00000406875]; 15049 bp linear mRNA; 1198 amino acids,
HIPK2-002 [ENST00000342645]; 2757 bp linear mRNA; 918 amino acids.

Pseudogene
Nothing known.

Protein

Description
HIPK2 is a protein kinase of 1198 amino acids (131 kDa); posttranslational modifications: phosphorylation, ubiquitination, sumoylation at K25, caspase cleavage at D916 and D977.
Contains several motifs and domains (from N- to C-terminus): a nuclear localisation signal (NLS1 (97-157), a kinase domain (192-520), an interaction domain for homeodomain transcription factors (583-798), a NLS2 (780-840) and a NLS3 within a speckle-retention signal (SRS) (860-967), a PEST sequence (839-934) and an autoinhibitory domain (935-1050).

Expression
HIPK2 is ubiquitously expressed (high mRNA levels in neuronal tissues, heart, muscle and kidney); but barely detectable at protein levels in unstressed cells. Protein levels increase upon genotoxic stress.

Localisation
Mainly nuclear localisation, in nuclear bodies; but also found in nucleoplasm and cytoplasm.

Function
HIPK2 is a potential tumour suppressor; in vivo data suggest at least a role as an haploinsufficient tumour suppressor in the skin of mice.
HIPK2 is a protein kinase that interacts with numerous transcription factors (such as p53, AML1(RUNX1), PAX6, c-MYB or NK3) as well as transcriptional
regulators (such as CBP, p300, Groucho, CtBP, HMGAI or Smads). In this way HIPK2 can activate or repress transcription and thereby influence differentiation, development and the DNA damage response.

HIPK2 is an unstable protein in unstressed cells. It is constantly degraded via the ubiquitin-proteasome system (mediated by the E3 ubiquitin ligases SIAH1/SIAH2, WSB1 and MDM2). Various types of DNA damage (e.g. UV, IR or chemotherapeutics) lead to stabilisation of the kinase and an HIPK2-mediated induction of apoptosis or presumably also senescence.

HIPK2 can promote the apoptotic program via p53-dependent and -independent pathways through phosphorylation of p53 at Ser46 or phosphorylation of the anti-apoptotic co-repressor CtBP at Ser422 (both actions leading to the transcription of pro-apoptotic target genes).

HIPK2 plays a role in the transcriptional regulation at low oxygen concentrations (hypoxia). Interestingly, HIPK2 also seems to have pro-survival functions, at least in dopamine neurons.

**Homology**

HIPK2 is conserved from flies to man.

**Mutations**

**Somatic**

HIPK2 is rarely mutated (2 out of 130 cases) in acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) patients. Two missense mutations (R868W and N958I) within the speckle-retention signal (SRS) were reported. These mutations led to a changed nuclear localisation of HIPK2 and a decreased transactivation potential in AML1- and p53-dependent transcription. The mutants showed dominant-negative effects (Li et al., 2007).

**Implicated in**

**Thyroid and breast cancer**

**Oncogenesis**

HIPK2 is frequently inactivated by transcriptional downregulation in thyroid carcinomas (8 out of 14 cases) and breast carcinomas (8 out of 20 cases) (Pierantoni et al., 2002).

**Breast cancer**

**Oncogenesis**

HIPK2 is inactivated on protein level by cytoplasmic relocalisation through HMGA1. Overexpression of HMGA1 was reported to inhibit p53-mediated apoptosis by removing HIPK2 from the nucleus and retaining it in the cytoplasm. Observations could be correlated with in vivo data, at least in breast cancer. WT p53-expressing breast carcinomas showed a low spontaneous apoptotic index in case of HIPK2-relocalisation (Pierantoni et al., 2007).

**Epithelial tumours (with altered beta4 integrin expression)**

**Oncogenesis**

HIPK2 was reported to repress beta4 integrin expression and thereby beta4-mediated tumour progression in a p53-dependent manner. Beta4 overexpression correlates in vivo with a cytoplasmic relocalisation of HIPK2, at least in breast cancer: HIPK2 showed a cytoplasmic pattern in 62.5% of the beta4-positive tumours (Bon et al., 2009).

**Juvenile pilocytic astrocytomas (JPA)**

**Note**

Benign childhood brain tumors.

**Disease**

A frequent amplification of HIPK2 along with BRAF rearrangements in JPA (35 out of 53 cases) through 7q34 duplication was reported. This duplication was more specific for JPA that originated from the cerebellum or the optic chiasm. It was absent in other brain tumours. If (and how) HIPK2 contributes to JPA development is currently unclear (Jacob et al., 2009).

**Cervical cancer**

**Note**

Surprisingly, a significant overexpression of HIPK2 in cervical cancer was reported. But if (and how) HIPK2 contributes to the development of cervical carcinomas remains unclear. No correlation between HIPK2 expression and grade or prognosis of the disease could be demonstrated so far (Al-Beiti et al., 2008).

**AML(RUNX1)-associated leukemias**

**Oncogenesis**

HIPK2 is inactivated on protein level by relocalisation through a PEBP2-beta-SMMHC fusion protein. Targeting of HIPK2 to cytoplasmic filaments and thereby prevention of AML1(RUNX1) activation was reported. Specifically, phosphorylation of RUNX1 and its cofactor p300 seems to be inhibited by HIPK2 relocalisation (Wee et al., 2008).

**References**


Hofmann TG, Mincheva A, Lichter P, Dröge W, Schmitz ML. Human homeodomain-interacting protein kinase-2 (HIPK2) is a member of the Dyrk family of protein kinases and maps to chromosome 7q32-q34. Biochimie. 2000 Dec;82(12):1123-7


Dauth I, Krüger J, Hofmann TG. Homeodomain-interacting protein kinase 2 is the ionizing radiation-activated p53 serine 46 kinase and is regulated by ATM. Cancer Res. 2007 Mar 1;67(5):2274-9


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