HTATIP (HIV-1 Tat interacting protein, 60kDa)

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Identity

Hugo: HTATIP

Other names: Tip60; Tip; 60kDa Tat interacting protein; HIV-1 Tat interacting protein; cPLA(2) interacting protein; iTip60; PLIP/Tip60b; Tip60a; Esa1; Hs.6364

Location: 11q13.1

DNA/RNA

The HTATIP gene consists of 14 exons. 7,586 bases.

Transcription

The predominant mRNA transcribed from this gene is 2,229 bp long. This is actually the isoform 2 of HTATIP.

Two others isoforms generated by alternative splicing have been described:
- Isoform 1 retains the alternatively spliced intron 1,
- Isoform 3 lacks exon 5.

Pseudogene

No pseudogene is currently known.

Protein

Description

The Tip60 protein (isoform 2) is 513 amino acids long and its molecular weight is about 60 kDa. It was cloned and characterized in 1996 thanks to its interaction with the HIV-1 transactivator Tat protein.

Isoform 1 produces a 546 amino acids long protein.

Isoform 3 produces a 461 amino acids long protein.

A novel isoform, Tip55, encodes a novel splicing variant corresponding to 103 amino acids of the C-terminus.

The domain architectures of human TIP60 is similar to yeast Esa1 protein and consist of a chromodomain and a MYST domain harboring a zinc finger and an Acetyl-CoA binding site.

Expression

Tip60 is ubiquitously expressed.

In mouse adult tissues Tip60 is expressed in the following decreasing order of intensity: testis, heart, brain, kidney, liver, lung, with little to no expression in spleen and skeletal muscle.

In human, Tip60 (Isoform 2) and PLIP (Isoform 3) are expressed in human heart, kidney and brain tissue.

With a half-life of approximately 30 minutes, Tip60 is very unstable. In normal conditions, the proteasome pathway permits to maintain low protein levels. Tip60 is ubiquitinatated and targeted to proteasome-mediated degradation by Mdm2 but also by p300-associated E4 ubiquitin ligase. Tip60 is stabilized after DNA damage, and accumulates in cells. Moreover, Tip60 is the target of several post-translational modifications such as phosphorylation on serine 86 and 90 by cdc2 but also acetylation by p300/CBP acetyltransferases.
Acetylation by p300/CBP occurs in the zinc finger of Tip60 but consequences of this modification are currently not known. Finally, a recent report shows that Tip60 is sumoylated at lysines 430 and 451 via Ubc9. No data are available about regulation of the Tip60 promoter.

**Localisation**
Tip60 (Isoform 2) is nuclear. PLIP (Isoform 3) is nuclear but also cytoplasmic.

**Function**
Tip60 is a Histone Acetyltransferase (HAT), which belongs to the MYST family. It participates in a multimolecular complex: The Tip60 complex, which contains proteins such as p400, Tip49a and Tip49b. Within this complex, Tip60 exerts its HAT activity on nucleosomal histone H4. Tip60 is involved in various cellular mechanisms:
- In transcription: Tip60 acts as a coactivator. Indeed, Tip60 is able to interact with transcription factors, such as E2F-1 or c-Myc. Tip60 can be recruited to Myc and E2F-1 target promoters and enhances Myc transactivation. It also acetylates histone H4 on several E2F responsive genes. Moreover Tip60 was found to be involved in nuclear receptor (NR) signaling and to be a NR-coregulator.
- In apoptosis and cell cycle arrest: Tip60 can interact with and acetylate the tumor suppressor p53. It enhances p53 binding to pro-apoptotic target genes like PUMA, Bax or Fas. Moreover, Tip60 is also required for cell growth arrest via the p21-dependent pathway.
- In DNA repair: Tip60 is involved in double strand breaks (DSB) repair. Interacting and acetylating ATM, Tip60 participates in DNA damage signaling. But, Tip60 is also involved directly in DSB repair since it is recruited, with TRRAP, to the DSB site. Tip60 interacts with the chromatin surrounding sites of DSBs and this recruitment is responsible for hyperacetylation of histone H4.

**Homology**
Tip60 CHROMO domain has been identified by sequence homology with the Heterochromatin-associated protein 1 (HP1) chromodomain, which recognizes methylated lysines. It also harbors the MYST domain, which is highly conserved from yeast to human.
Homologs in other species:
- S. Cerevisiae: Esa1
- D. Melanogaster: DmeI/Tip60
- M. musculus: Htatip
- R. norvegicus: Htatip
Predicted:
- P. troglodytes: HTATIP
- M. mulatta: HTATIP

**Mutations**
Note: No mutation in Tip60 protein has been currently described.

**Implicated in**

**Acquired Immunodeficiency Syndrome (AIDS)**

**Disease**
Tip60 interacts with the HIV-1 transactivator Tat and this interaction inhibits Tip60 HAT activity. Moreover, in Jurkat cells, Tat enhances Tip60 turnover since it uses the p300/CBP-associated E4-type ubiquitin-ligase...
activity to induce polyubiquitynation and degradation of Tip60. This targeting by Tat induces an impairment of Tip60-dependent apoptosis after DNA damage.

**Neurodegenerative diseases:**

**Alzheimer’s disease**

**Disease**

In the nucleus of human H4 neuroglioma cells, Tip60 can interact with a free carboxyl-terminal intracellular fragment, APP-CT, which is generated by the cleavage of the Amyloid precursor protein APP by a gamma-secretase. This fragment induces apoptosis of neuroglioma and this cell death is enhanced when a wild type form of Tip60 is transfected. Thus Tip60 might play a role in Alzheimer’s disease neurodegeneration.

**Spinocerebellar ataxia type-1**

**Disease**

Tip60 participates in a complex with ATXN1 and ROR-alpha in a conditional transgenic mouse model of Spinocerebellar ataxia type-1 (SCA1), one of the nine inherited polyglutamine neurodegenerative diseases.

**Cancers:**

**Prostate cancer**

**Disease**

Immunohistochemistry experiments have shown that Tip60 accumulates in the nucleus of hormone-refractory prostate cancer compared to prostate hyperplasia and primary prostate cancer.

**Lung cancer and colon cancer**

**Disease**

Real time RT-PCR experiments have shown that Tip60 mRNA is under expressed in colon and lung carcinomas.

**Skin cancer**

**Disease**

The expression levels of Tip60 protein, analyzed by western blot, were found to be greater in skin tumors as compared to adjacent non-tumor-bearing skin in a skin cancer mouse model (K6/ODC mouse). Additionally, the interaction between Tip60 and E2F1 is enhanced in these tumors.

**HTLV-1 induced leukemogenesis**

**Disease**

Enhancement of c-Myc transforming activity by HTLV-1 p30II oncprotein in HeLa cells requires TIP60 HAT activity.

**References**


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