

Gene Section Review

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

Lise Mattera

Dr Trouche Team, LBCMCP, UMR 5088 CNRS, 118 route de Narbonne, 31062 Toulouse cedex 9, France

Published in Atlas Database: October 2007

Online updated version: <http://AtlasGeneticsOncology.org/Genes/HTATIPID40893ch11q13.html>

DOI: 10.4267/2042/38522

This work is licensed under a Creative Commons Attribution-Non-commercial-No Derivative Works 2.0 France Licence.
© 2008 Atlas of Genetics and Cytogenetics in Oncology and Haematology

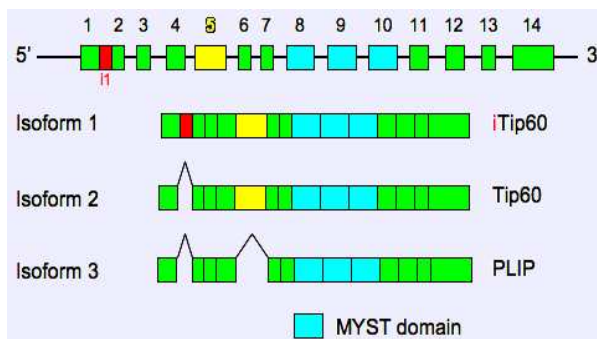
Identity

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



Description

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.

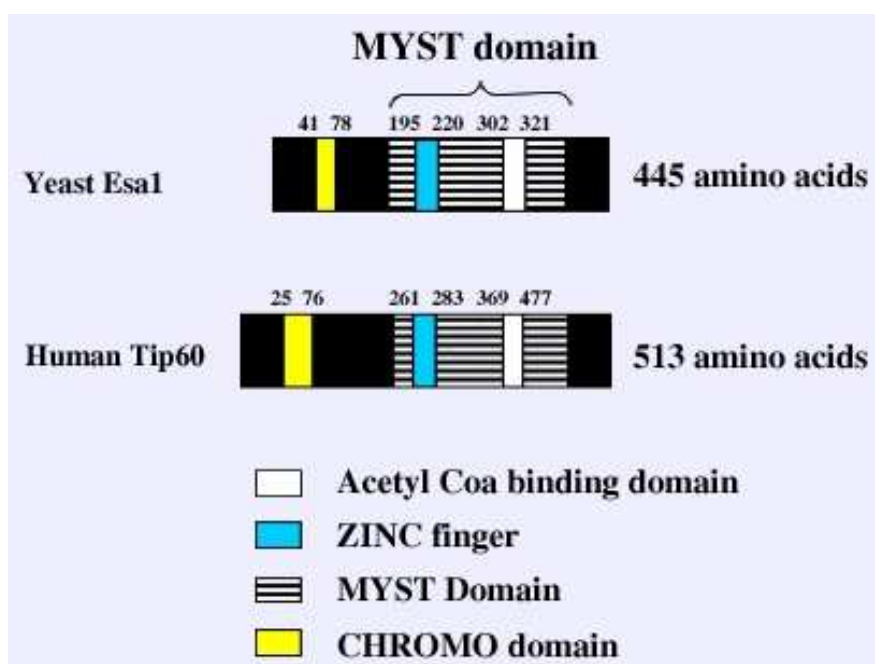
Expression

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 ubiquitinated 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 oncoprotein in HeLa cells requires TIP60 HAT activity.

References

Kamine J, Elangovan B, Subramanian T, Coleman D, Chinnadurai G. Identification of a cellular protein that

specifically interacts with the essential cysteine region of the HIV-1 Tat transactivator. *Virology* 1996;216(2):357-366.

Brady ME, Ozanne DM, Gaughan L, Waite I, Cook S, Neal DE, Robson CN. Tip60 is a nuclear hormone receptor coactivator. *J Biol Chem* 1999;274(25):17599-17604.

Creaven M, Hans F, Mutskov V, Col E, Caron C, Dimitrov S, Khochbin S. Control of the histone-acetyltransferase activity of Tip60 by the HIV-1 transactivator protein, Tat. *Biochemistry* 1999;38(27):8826-8830.

Ikura T, Ogryzko VV, Grigoriev M, Groisman R, Wang J, Horikoshi M, Scully R, Qin J, Nakatani Y. Involvement of the TIP60 histone acetylase complex in DNA repair and apoptosis. *Cell* 2000;102(4):463-473.

Ran Q, Pereira-Smith OM. Identification of an alternatively spliced form of the Tat interactive protein (Tip60), Tip60(beta). *Gene* 2000;258(1-2):141-146.

Gaughan L, Brady ME, Cook S, Neal DE, Robson CN. Tip60 is a co-activator specific for class I nuclear hormone receptors. *J Biol Chem* 2001;276(50):46841-46848.

Sheridan AM, Force T, Yoon HJ, O'Leary E, Choukroun G, Taheri MR, Bonventre JV. PLIP, a novel splice variant of Tip60, interacts with group IV cytosolic phospholipase A(2), induces apoptosis, and potentiates prostaglandin production. *Mol Cell Biol* 2001;21(14):4470-4481.

Gaughan L, Logan IR, Cook S, Neal DE, Robson CN. Tip60 and histone deacetylase 1 regulate androgen receptor activity through changes to the acetylation status of the receptor. *J Biol Chem* 2002;277(29):25904-25913.

Kinoshita A, Whelan CM, Berezovska O, Hyman BT. The gamma secretase-generated carboxyl-terminal domain of the amyloid precursor protein induces apoptosis via Tip60 in H4 cells. *J Biol Chem* 2002;277(32):28530-28536.

Legube G, Linares LK, Lemercier C, Scheffner M, Khochbin S, Trouche D. Tip60 is targeted to proteasome-mediated degradation by Mdm2 and accumulates after UV irradiation. *EMBO J* 2002;21(7):1704-1712.

McAllister D, Merlo X, Lough J. Characterization and expression of the mouse tat interactive protein 60 kD (TIP60) gene. *Gene* 2002;289(1-2):169-176.

Frank SR, Parisi T, Taubert S, Fernandez P, Fuchs M, Chan HM, Livingston DM, Amati B. MYC recruits the TIP60 histone acetyltransferase complex to chromatin. *EMBO Rep* 2003;4(6):575-580.

Halkidou K, Gnanapragasam VJ, Mehta PB, Logan IR, Brady ME, Cook S, Leung HY, Neal DE, Robson CN. Expression of Tip60, an androgen receptor coactivator, and its role in prostate cancer development. *Oncogene* 2003;22(16):2466-2477.

Legube G, Trouche D. Identification of a larger form of the histone acetyl transferase Tip60. *Gene* 2003;310:161-168.

Lemercier C, Legube G, Caron C, Louwagie M, Garin J, Trouche D, Khochbin S. Tip60 acetyltransferase activity is controlled by phosphorylation. *J Biol Chem* 2003;278(7):4713-4718.

Berns K, Hijmans EM, Mullenders J, Brummelkamp TR, Velds A, Heimerikx M, Kerkhoven RM, Madiredjo M, Nijkamp W, Weigelt B, Agami R, Ge W, Cavet G, Linsley PS, Beijersbergen RL, Bernards R. A large-scale RNAi screen in human cells identifies new components of the p53 pathway. *Nature* 2004;428(6981):431-437.

Legube G, Linares LK, Tyteca S, Caron C, Scheffner M, Chevillard-Briet M, Trouche D. Role of the histone acetyl transferase Tip60 in the p53 pathway. *J Biol Chem* 2004;279(43):44825-44833.

Taubert S, Gorrini C, Frank SR, Parisi T, Fuchs M, Chan HM, Livingston DM, Amati B. E2F-dependent histone acetylation

and recruitment of the Tip60 acetyltransferase complex to chromatin in late G1. *Mol Cell Biol* 2004;24(10):4546-4556.

Awasthi S, Sharma A, Wong K, Zhang J, Matlock EF, Rogers L, Motloch P, Takemoto S, Taguchi H, Cole MD, Lüscher B, Dittrich O, Tagami H, Nakatani Y, McGee M, Girard AM, Gaughan L, Robson CN, Monnat RJ Jr, Harrod R. A human T-cell lymphotropic virus type 1 enhancer of Myc transforming potential stabilizes Myc-TIP60 transcriptional interactions. *Mol Cell Biol* 2005;25(14):6178-6198.

Col E, Caron C, Chable-Bessia C, Legube G, Gazzeri S, Komatsu Y, Yoshida M, Benkirane M, Trouche D, Khochbin S. HIV-1 Tat targets Tip60 to impair the apoptotic cell response to genotoxic stresses. *EMBO J* 2005;24(14):2634-2645.

Sun Y, Jiang X, Chen S, Fernandes N, Price BD. A role for the Tip60 histone acetyltransferase in the acetylation and activation of ATM. *Proc Natl Acad Sci USA* 2005;102(37):13182-13187.

Hobbs CA, Wei G, Defeo K, Paul B, Hayes CS, Gilmour SK. Tip60 Protein Isoforms and Altered Function in Skin and Tumors that Overexpress Ornithine Decarboxylase. *Cancer Res* 2006;66(16):8116-8122.

Kim MS, Merlo X, Wilson C, Lough J. Co-activation of atrial natriuretic factor promoter by Tip60 and serum response factor. *J Biol Chem* 2006;281(22):15082-15089.

LLeonart ME, Vidal F, Gallardo D, Diaz-Fuertes M, Rojo F, Cuatrecasas M, López-Vicente L, Kondoh H, Blanco C, Carnero A, Ramón y Cajal S. New p53 related genes in human tumors: significant downregulation in colon and lung carcinomas. *Oncol Rep* 2006;16(3):603-608.

Murr R, Loizou JI, Yang YG, Cuenin C, Li H, Wang ZQ, Herceg Z. Histone acetylation by Trrap-Tip60 modulates loading of

repair proteins and repair of DNA double-strand breaks. *Nat Cell Biol* 2006;8(1):91-99.

Serra HG, Duvick L, Zu T, Carlson K, Stevens S, Jorgensen N, Lysholm A, Burrigh E, Zoghbi HY, Clark HB, Andresen JM, Orr HT. RORalpha-mediated Purkinje cell development determines disease severity in adult SCA1 mice. *Cell* 2006;127(4):697-708.

Sykes SM, Mellert HS, Holbert MA, Li K, Marmorstein R, Lane WS, McMahon SB. Acetylation of the p53 DNA-binding domain regulates apoptosis induction. *Mol Cell* 2006;24(6):841-851.

Tang Y, Luo J, Zhang W, Gu W. Tip60-dependent acetylation of p53 modulates the decision between cell-cycle arrest and apoptosis. *Mol Cell* 2006;24(6):827-839.

Tyteca S, Vandromme M, Legube G, Chevillard-Briet M, Trouche D. Tip60 and p400 are both required for UV-induced apoptosis but play antagonistic roles in cell cycle progression. *EMBO J* 2006;25(8):1680-1689.

Cheng Z, Ke Y, Ding X, Wang F, Wang H, Ahmed K, Liu Z, Xu Y, Aikhionbare F, Yan H, Liu J, Xue Y, Powell M, Liang S, Reddy SE, Hu R, Huang H, Jin C, Yao X. Functional characterization of TIP60 sumoylation in UV-irradiated DNA damage response. *Oncogene* 2007 Aug 20;[Epub ahead of print].

This article should be referenced as such:

Mattera L. HTATIP (HIV-1 Tat interacting protein, 60kDa). *Atlas Genet Cytogenet Oncol Haematol*.2008;12(3):213-216.
