

Gene Section

Mini Review

EP400 (E1A binding protein p400)

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Identity

Hugo: EP400

Other names: CAGH32; E1A binding protein p400; hDomino; p400; TNRC12

Location: 12q24.33

DNA/RNA

Description

The EP400 gene consists of 52 exons and spans 130.5 kb of genomic sequence on chromosome 12.

Transcription

The predominant mRNA transcribed from this gene is 12,265 nt long. This is actually the isoform 2 of EP400. Three other isoforms generated by alternative splicing have been described:

Isoform 1 retains an alternatively spliced sequence inside intron 2.

Isoform 3 lacks exon 4.

Isoform 4 lacks exon 23.

Pseudogene

There is an EP400 pseudogene termed 'EP400 N-terminal like' (EP400-NL) in the same locus.

Protein

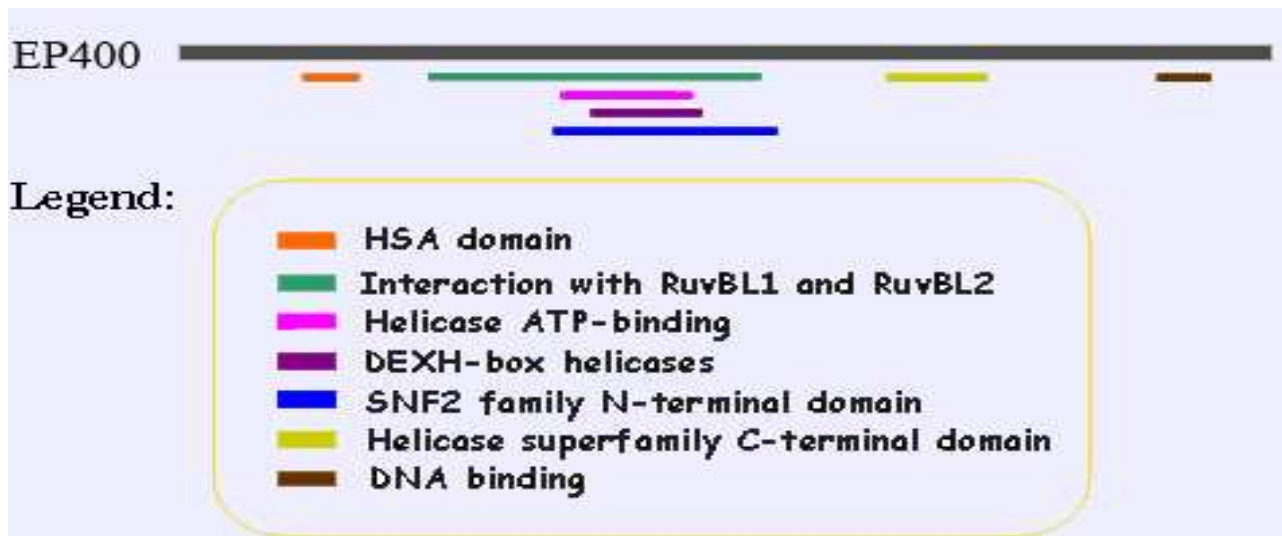
Description

The EP400 protein (isoform 2) is 3124 amino acids long and its molecular weight is about 400 kDa. It was cloned and characterized in 2001 thanks to its interaction with the E1A oncoprotein.

Isoform 1 produces a 3160 aa long protein.

Isoform 3 produces a 3087 aa long protein.

Isoform 4 produces a 3043 aa long protein.



There has been no experimental confirmation for isoforms 3 and 4.

The only described post-translational modification is a phosphorylation on Ser736.

Expression

No data.

Localisation

EP400 belongs to chromatin remodelling complexes which are located in the nucleus, so it is probably nuclear. However, its cellular localization has not been formally monitored to date.

Function

EP400 belongs to the SWI2/SNF2 family of ATPases and is found in two highly related chromatin remodelling complexes: the Tip60 and p400 complexes. In these complexes, EP400 is associated with other enzymes such as the Tip60 histone acetyltransferase and/or the RuvBL1 and RuvBL2 helicases. (Note: putative specific functions of each splicing variant have not been investigated to date)

Functions at the cellular level:

EP400 has been implicated in cell cycle control, apoptosis and development.

First, the depletion of EP400 in untransformed human fibroblasts leads to senescence through induction of the p53 - p21 pathway. Likewise, the EP400 knock-down induces a p21-dependent cell cycle arrest in human cell lines. According to these results, EP400 seems to favour cell proliferation.

On the other hand, EP400 is required for E1A-mediated apoptosis. Similarly, EP400 is required for apoptosis upon DNA damage in human cell lines. Thus, EP400 also favours apoptosis, possibly through preventing cell cycle arrest.

Finally, the murine homolog of EP400 appears to be involved in embryonic hematopoiesis.

Functions at the molecular level:

EP400 has ATP-dependent chromatin remodelling activity. Accordingly, EP400 was shown to be recruited along with the Tip60 complex on promoters by the c-myc and E2F transcription factors. Moreover, the EP400 homolog in drosophila is able to exchange specific histone variants at double-strand breaks.

Homology

EP400 contains the SNF2 N-terminal domain shared by all ATPases of the SWI2/SNF2 family (SNF2, STH1, RAD16, RAD54, ISWI...). It also bears helicase-specific domains (see diagram):

an helicase C-terminal domain;

an HSA domain;

a DEXH box which contains the ATP-binding region.

Putative homologs in other species (non exhaustive):

M. musculus: Ep400

R. norvegicus: Ep400

G. gallus: EP400

D. melanogaster: DOM or domino

Implicated in

Cancers

Oncogenesis

It was shown that EP400 is a target for the E1A viral oncoprotein transforming activity.

Indeed, studies showed that the overexpression of specific EP400 fragments corresponding to the E1A binding region (the SWI2/SNF2 domain) enhance the ability of E1A to transform rat embryo fibroblasts in the presence of ras. Moreover, the same fragments are able to partially restore the transforming activity of a transformation-defective E1A mutant.

References

- Fuchs M, Gerber J, Drapkin R, Sif S, Ikura T, Ogryzko V, Lane WS, Nakatani Y, Livingston DM. The p400 complex is an essential E1A transformation target. *Cell* 2001;106(3):297-307.
- 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.
- Beausoleil SA, Jedrychowski M, Schwartz D, Elias JE, Villen J, Li J, Cohn MA, Cantley LC, Gygi SP. Large-scale characterization of HeLa cell nuclear phosphoproteins. *Proc Natl Acad Sci USA* 2004;101(33):12130-12135.
- Kusch T, Florens L, Macdonald WH, Swanson SK, Glaser RL, Yates JR 3rd, Abmayr SM, Washburn MP, Workman JL. Acetylation by Tip60 is required for selective histone variant exchange at DNA lesions. *Science* 2004;306(5704):2084-2087.
- Chan HM, Narita M, Lowe SW, Livingston DM. The p400 E1A-associated protein is a novel component of the p53 --> p21 senescence pathway. *Genes Dev* 2005;19(2):196-201.
- Samuelson AV, Narita M, Chan HM, Jin J, de Stanchina E, McCurrach ME, Narita M, Fuchs M, Livingston DM, Lowe SW. p400 is required for E1A to promote apoptosis. *J Biol Chem* 2005;280(23):21915-21923.
- 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.
- Flinterman MB, Mymryk JS, Klanrit P, Yousef AF, Lowe SW, Caldas C, Gaken J, Farzaneh F, Tavassoli M. p400 function is required for the adenovirus E1A-mediated suppression of EGFR and tumour cell killing. *Oncogene* 2007;[Epub ahead of print].
- Ueda T, Watanabe-Fukunaga R, Ogawa H, Fukuyama H, Higashi Y, Nagata S, Fukunaga R. Critical role of the p400/mDomino chromatin-remodeling ATPase in embryonic hematopoiesis. *Genes Cells* 2007;12(5):581-592.

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