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Gene Section
Review

PPP1R8 (protein phosphatase 1, regulatory (inhibitor) subunit 8)

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Identity

Other names: ARD-1; ARD1; NIPP-1; NIPP1; PRO2047

HGNC (Hugo): PPP1R8

Location: 1p35.3

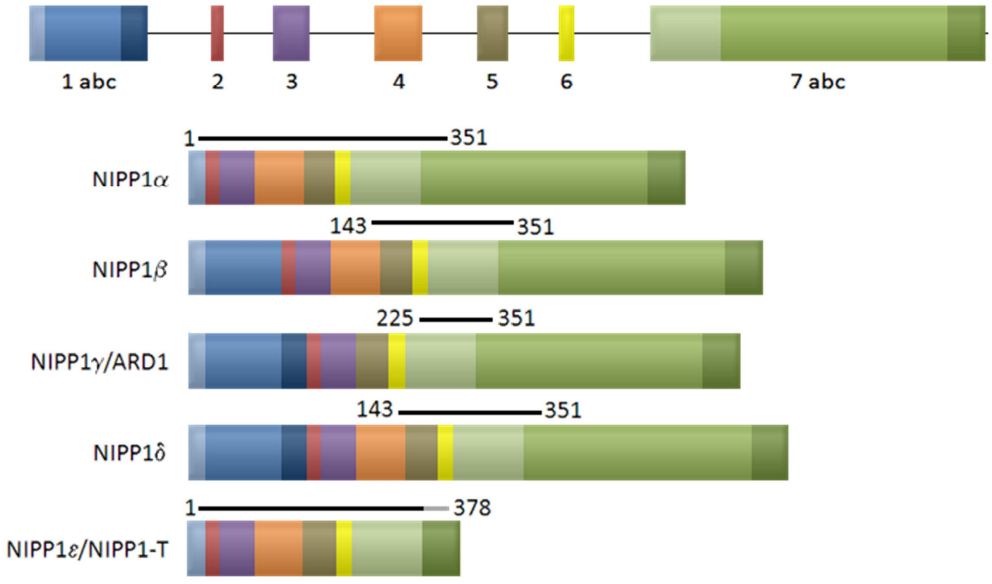
DNA/RNA

Note

ARD1 is a frequently used alias for NIPP1, however, this name actually corresponds to an alternative transcript (NIPP1gamma), which encodes a truncated form of NIPP1 encompassing residues 225-351 only. This transcript has been shown to restore endoribonuclease activity to E. coli rne gene mutants (Wang and Cohen, 1994; Claverie-Martin et al., 1997; Chang et al., 1999; Jin et al., 1999; Van Eynde et al., 1999). Moreover, note that the name ARD1 is also used for a completely unrelated protein, TRIM23 (Mishima et al., 1993).

Description

The entire PPP1R8 gene spans 20.9 kb on the forward strand of the long arm on chromosome 1. The gene contains 7 exons of which exon 1 has 5'-alternative splice sites.



Genomic organization of the PPP1R8 gene and the alternative splice variants with their corresponding coding sequences (black line). Exons and alternative splice sites are indicated by different colors.

Transcription

The PPP1R8 gene contains 7 exons which give rise to 5 alternative splice products (see diagram above).
When speaking about NIPP1, one usually refers to the NIPP1alpha isoform (39 kDa, 351 residues) which is by far the most abundant isoform in all examined mammalian tissues. When visualized by immunoblotting with C-terminal antibodies (which recognize all isoforms except NIPP1epsilon), also smaller polypeptides are visualized albeit at a much lower intensity as compared to the alpha-isoform. However, it is not clear yet whether these represent some of the other NIPP1 isoforms or simply degradation products of NIPP1alpha (Van Eynde et al., 1999; Chang et al., 1999; Fardilha et al., 2004).

Pseudogene

A processed pseudogene, termed PPP1R8P, has been mapped to chromosome 1p33-32 (48790762-48791795 bp from pter according to hg19 - Feb 2009). Consistent with this notion, it is only 1034 bp in size, contains no introns and encodes an incomplete NIPP1-transcript due to the presence of various premature stop codons (Van Eynde et al., 1999).

Protein

Note

Nuclear Inhibitor of PP1 (NIPP1) was first identified in bovine thymus nuclei as a potent inhibitor of the protein Ser/Thr phosphatase PP1 (Beullens et al., 1992; Beullens et al., 1993). Later on, it became clear that NIPP1 exerts various functions in the eukaryotic cell by serving as a kind of scaffold protein onto which a variety of proteins can bind. These interaction partners range from protein kinase MELK, protein phosphatase PP1 (PPP1C-a/PPP1C-b/PPP1C-c), the pre-mRNA splicing factors SAP155 (SF3B1) and CDC5L to the chromatin modifiers EED and EZH2.

Description

NIPP1 consists of 351 amino acids and has a molecular mass of 39 kDa. However, it migrates at a size of about 45 kDa on SDS-PAGE. NIPP1 contains an N-terminal ForkHead Associated (FHA) domain.
Via this established phosphothreonine-binding domain, NIPP1 interacts with protein kinase MELK, the splicing factors SAP155 and CDC5L and the histone methyltransferase EZH2. Moreover, it was shown that the NIPP1 FHA-domain binds to its ligands via phosphorylated TP-dipeptide motifs, present in the interacting proteins (Boudrez et al., 2000; Boudrez et al., 2002; Vulsteke et al., 2004; Nuytten et al., 2008).
Two additional interactors, PP1 and EED, have two separate binding sites on NIPP1: one in the central domain and the other at the C-terminus. In the central domain, the binding of NIPP1 to PP1 is mediated by a so called RVXF-motif, which is present in about two thirds of all known PP1 interacting proteins (Beullens et al., 1999; Beullens et al., 2000; Hendrickx et al., 2009). In addition, the C-terminal 22 residues can interact with nucleic acids (Jin et al., 1999).

Expression

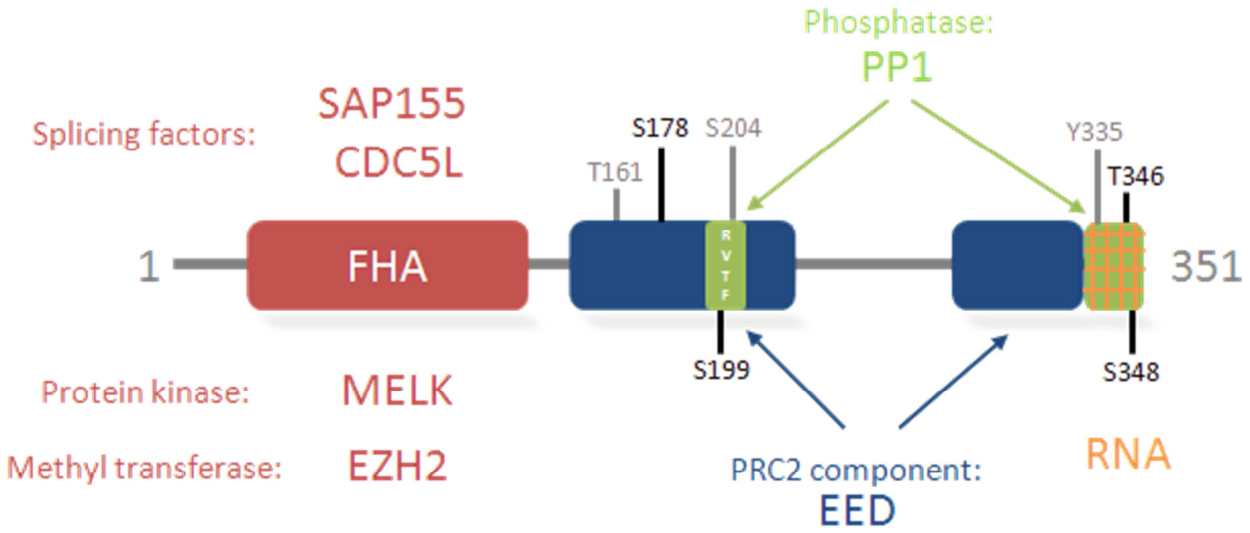
NIPP1 is ubiquitously expressed (Van Eynde et al., 1995).

Localisation

NIPP1 is a nuclear protein and is enriched in splicing factor storage sites called speckles (Trinkle-Mulcahy et al., 1999; Jagiello et al., 2000). Although largely nuclear, some data suggest that there also exists a cytoplasmic pool of NIPP1 (Boudrez et al., 1999; Jagiello et al., 1997).

Function

NIPP1 is a scaffold protein and exerts its functions via its interacting proteins. NIPP1 was discovered as a potent inhibitor and a major nuclear interactor of the phosphatase PP1 (Beullens et al., 1999). PP1 functions as a holoenzyme in which the interacting proteins confine substrate specificity, activity and/or localization of PP1 (Bollen et al., 2010). For NIPP1, it has been shown that it acts as a physiological PP1 inhibitor for some substrates, while functioning as an activator towards other substrates (Parker et al., 2002; Lesage et al., 2004; Comerford et al., 2006; Shi and Manley, 2007).
Also, the interaction between NIPP1 and PP1 can be regulated by phosphorylation (Beullens et al., 1993; Van Eynde et al., 1994; Jagiello et al., 1995; Vulsteke et al., 1997; Beullens et al., 1999). NIPP1 is also involved in 3 other major cellular processes: splicing, transcription and development. Firstly, NIPP1 is associated with spliceosomes and splicing factor storage sites called "speckles", probably mediated by its interaction with the splicing factors CDC5L and SAP155 (Boudrez et al., 2000; Deckert et al., 2006). Pre-mRNA splicing assays showed that NIPP1 is required for late stage spliceosome formation (Beullens and Bollen, 2002). Recently it was published that NIPP1 directs associated PP1 to dephosphorylate SAP155 (Tanuma et al., 2008). Secondly, NIPP1 is a transcriptional repressor via its interaction with EED and EZH2 (Jin et al., 2003; Roy et al., 2007), two core components of the Polycomb repressive complex 2 (PRC2). Through its interaction with PRC2, NIPP1 directs it to a subset of Polycomb target genes, where the methyltransferase EZH2 will mark genes proned for silencing by trimethylating histone 3 on lysine 27 (Nuytten et al, 2008). In 2010, Van Dessel et al. showed that this targeting function of NIPP1 is dependent on associated PP1. Finally, NIPP1 is essential for embryonic development as a NIPP1 knock out mouse is embryonically lethal at the onset of gastrulation (Van Eynde et al., 2004).



A schematic representation of the domain structure of NIPP1 and its interactor binding sites. The FHA-domain (red) binds the indicated interactors via a phosphorylated TP dipeptide motif. NIPP1 binds PP1 via the indicated RVXF-motif and via a C-terminal binding site (green). EED and RNA binding sites are colored blue and orange, respectively. Known phosphorylation sites are indicated in black (in vivo validated) or grey (in vitro data).

The splice variant NIPP1gamma or ARD1 displays a site-specific Mg^{2+}-dependent endoribonuclease activity, in contrast to the NIPP1alpha isoform, which does not possess this function (Wang and Cohen, 1994; Claverie-Martin et al., 1997; Chang et al., 1999; Jin et al., 1999; Van Eynde et al., 1999).

Homology

NIPP1 is highly conserved in all multicellular organisms.

Implicated in

Hepatoma

Disease

Cancer.

Prognosis

An increase in NIPP1 mRNA is correlated with a malignant phenotype in rats (Kim et al., 2000).

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