PTBP1 (polypyrimidine tract binding protein 1)
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Identity
Other names: HNRNP-I, HNRNPI, HNRPI, PTB, PTB-1, PTB-T, PTB2, PTB3, PTB4, pPTB
HGNC (Hugo): PTBP1
Location: 19p13.3

DNA/RNA
Description
The PTBP1 locus spans 14936 bases on the short arm of chromosome 19 and is composed of 14 exons.

Transcription
PTBP1 results from skipping of exon 9 (3203 bp mRNA and 531 amino acid protein). Three additional isoforms are generated by alternative splicing: PTBP2 (3260 bp mRNA and 550 amino acid protein) and PTBP4 (3281 mRNA protein and 557 amino acid protein) derive from exon 9 inclusion using two alternative 3' splice sites, while PTB-T has been reported to result from alternative splicing of exons 2-10 (Sawicka et al., 2004).

Pseudogene
PTBP1P (polypyrimidine tract binding protein 1 pseudogene), chromosome location 14q23.3, starts at 65745938 and ends at 65748375 bp from pter (according to hg19-Feb_2009).

Protein
Description
57 kDa protein belonging to the heterogeneous nuclear ribonucleoprotein family (hnRNP). PTBP1 has four RNA recognition motifs (RRMs) and a conserved N-terminal domain that harbors both nuclear localisation and export signals (NLS and NES).
Through the RRM, PTBP1 binds to the transcript at multiple sites within large pyrimidine tracts leading to conformational changes suitable for functional mRNA processing (Sawicka et al., 2004).
**Expression**

PTBP1 is ubiquitously expressed in human tissues emerging as a pleiotropic splicing regulator. PTBP1 expression levels have been associated with myoblast and neural precursor differentiation through specific modulation of the splicing pattern (Clower et al., 2010). In the brain, in particular, the switch from PTBP1 to nPTB expression drives the differentiation towards the neuronal lineage: PTBP1 is expressed in neural precursors and glial cells, while post-mitotic neurons express only nPTB (Boutz et al., 2007). Recently a strong PTBP1 expression has been found in embryonic stem cells, particularly those in the brain cortex and subventricular zone, where PTBP1 appears essential for cell division after implantation (Shibayama et al., 2009; Suckale et al., 2011).

**Localisation**

PTBP1 shuttles between the nucleus and the cytoplasm. Cytoplasmic localisation is mainly achieved by PKA-mediated phosphorylation of a specific serine residue (Ser-16) within the nuclear localisation signal. Cytoplasmic accumulation of PTB occurs during cell stress (Sawicka et al., 2008). PTBP1 has also been identified as a key component in maintaining the integrity of the perinucleolar compartment, a sub-nuclear structure predominantly found in transformed cells (Wang et al., 2003).

**Function**

PTB was originally identified as a regulator of alternative splicing (Garcia-Blanco et al., 1989) but other roles in mRNA processing have been described (Sawicka et al., 2008).

**Alternative splicing regulation:** PTBP1 commonly acts as repressor of alternative splicing favouring skipping of alternative exons. Different models of PTBP1 activity have been proposed (Spellman and Smith, 2006): 1) binding competition with the splicing factor U2AF65 at the 3’ splice site of alternative exons; 2) polymerization of PTBP1 molecules on the alternative exon masking splicing enhancer sequences; and 3) looping out of alternative exon by PTBP1 binding of flanking intronic sequences. Targets of PTBP1-mediated repression of exon inclusion comprise α-tropomiosin, α-actinin, GABAγ2 (gamma-aminobutyric acid γ2), c-src and FGFR2 (fibroblast growth factor receptor 2) (Li et al., 2007; Spellman et al., 2005). Recent evidences indicate that PTBP1 may also favour exon inclusion depending on the position of its binding sites relative to the target exon. Upon binding to the upstream intron and/or within the exon, PTBP1 represses exon inclusion, while by binding to the downstream intron, it activates exon inclusion. The PTBP1 position-dependent activity relies on the splice site features: in particular included exons show weaker 5’ splice sites, whereas skipped exons have longer polypyrimidine tracts (Lorian et al., 2010).

**3’-end processing:** PTBP1 both promotes and inhibits the mRNA 3’-end cleavage required for polyadenylation. PTBP1 may prevent mRNA polyadenylation through competition with the cleavage stimulating factor (CstF), or stimulate polyadenylation by binding to pyrimidine-rich upstream elements (USEs).

**mRNA transport:** evidences for a role of PTBP1 in mRNA transport come from experiments in Xenopus, where the PTBP1 homologue (VgRBP60) is involved in the localisation of the Vg1 mRNA. In vertebrates PKA-activated PTBP1 is involved in α-actin mRNA localisation at neurite terminals.

**mRNA stability:** PTBP1 increases the stability of specific transcript by binding to the untranslated regions of mRNA and consequently competing with factors involved in mRNA degradation. Transcripts with PTB-mediated increased stability include those of insulin, VEGF (vascular endothelial growth factor), CD154 (cluster of differentiation 154) and iNOS (inducible nitric oxide synthase).

**Viral translation and replication:** PTBP1 acts as an ITAF (IRES -internal ribosomal entry site- trans-acting factor) for mRNA translation of virus belonging to the Picornaviridae family and lacking cap structure. PTBP1 seems to have a role as a viral RNA chaperone that stabilizes or alters IRES structure to direct ribosomes to the correct start codon. **IRES-mediated translation:** PTBP1 favours cap-independent translation of few cellular RNAs under...
cell stress, apoptosis or infection through ribosome recruitment to IRES. In this case, PTBP1 cytoplasmic relocalisation is required.

**Homology**

PTBP1 shares 70-80% homology with two other proteins: nPTB (neural PTB), expressed in adult brain, muscle and testis, and ROD1 (regulator of differentiation 1) only expressed in hematopoietic cells. PTB also regulates alternative splicing of its homologues, in particular the nonsense-mediated decay of nPTB transcripts and the non-productive splicing of ROD1 (Sawicka et al., 2008).

**Mutations**

**Somatic**

Three synonymous mutations have been reported in cancer samples: c.510C>T (p.A170A) in kidney carcinoma (Dalgliesh et al., 2010), c.1416C>T (p.F472F) in melanoma (Wei et al., 2011) and c.501G>A (p.S167S) in squamous cell carcinoma of the mouth (Stransky et al., 2011). Moreover five missense mutations have been identified in other cancer samples: c.932C>T (p.A311V) in ovarian carcinoma (Cancer Genome Atlas Research Network, 2011), c.413C>T (p.T138I) in skin squamous cell carcinoma (Durinck et al., 2011), c.212C>T (p.T71M), c.666C>G (p.F222L) and c.928G>A (p.G310R) in squamous cell carcinomas of the mouth and larynx (Durinck et al., 2011; Stransky et al., 2011).

**Implicated in**

**Glioma**

**Note**

PTBP1 is aberrantly overexpressed in glioma with expression levels correlated with glial cell transformation. The increased expression of PTBP1 contributes to gliomagenesis by deregulating the alternative splicing of genes involved in cell proliferation and migration (McCutcheon et al., 2004; Cheung et al., 2006; Cheung et al., 2009). FGFR-1 (fibroblast growth factor receptor-1): PTBP1 overexpression increases FGFR-1 α-exon skipping and hence the synthesis of a receptor with higher affinity for fibroblast growth factor, favouring transformed cell growth (Jin et al., 2000).

PKM (pyruvate kinase): PTBP1 overexpression leads to the re-expression of the embryonic pyruvate kinase isoform, PKM2, in transformed glial cells. The switch from PKM1, normally expressed in terminally differentiated cells, to PKM2 is achieved through the PTBP1-mediated inclusion in the PKM mRNA of exon 10, instead of exon 9. In transformed cells PKM2 promotes aerobic glycolysis and proliferation. Recently c-Myc overexpression has been demonstrated to upregulate PTBP1 transcription in transformed glial cells (David et al., 2010).

USP5 (ubiquitin specific peptidase 5): PTBP1 overexpression in GBM forces the expression of USP5 isoform 2, a protein involved in ubiquitination. USP5 isoform 2 has a low activity and favours cell growth and migration (Izaguirre et al., 2011).

**Ovarian tumour**

**Note**

PTBP1 is overexpressed in the majority of epithelial ovarian tumours and deregulates cell proliferation, anchorage-dependent growth and invasiveness. PTBP1 targets in ovarian transformed cells have not yet been identified (He et al., 2007).

**Alzheimer's disease (AD)**

**Note**

Recent evidences delineate PTBP1 as a regulator of the amyloid precursor protein (APP) in neurons. In particular, PTBP1 altered expression in neuronal cells, likely mediated by miR-124, enhances the expression of APP isoforms including exon 7 and/or 8. These isoforms have been found enriched in AD patients and associated with β-amyloid production (Smith et al., 2011).

**References**


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