PPP1R9B (protein phosphatase 1, regulatory subunit 9B)

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Identity

Other names: PPP1R6, PPP1R9, SPINO, Spn
HGNC (Hugo): PPP1R9B
Location: 17q21.33

DNA/RNA

See the scheme of the 17q21 locus below.

Protein

Description

PPP1R9B protein have different modular domains that govern protein-protein interactions (Sarrouilhe et al., 2006). These domains include two F-actin-, three potential Src homology 3 (SH3)-, one receptor- and one PP1-binding domains, one PDZ binding domain, three coiled-coil domains, and one potential leucine/isoleucine zipper motif.

Many partner proteins of PPP1R9B have been described, including enzymes, guanine nucleotide exchange factors, cytoskeletal and cell adhesion molecules, membrane receptors, ion channels and G-protein signaling protein regulators. PPP1R9B also regulates seven-transmembrane receptor signaling and may link these receptors to intracellular mitogenic signaling dependent on p70S6k and the Rac-GEF. Accordingly, PPP1R9B may serve as a linker between actin cytoskeleton and transmembrane proteins, targeting PP1 to its targets and facilitating the coordination of the external signaling with the downstream pathway (Brady et al., 2003; Küntziger et al., 2011; Sarrouilhe et al., 2006; Vivo et al., 2001; Wang et al., 2004; Carnero, 2012).

Scheme of the 17q21 locus. Adapted from Carnero, 2012.
PPP1R9B (protein phosphatase 1, regulatory subunit 9B) Carnero A

Expression

PPP1R9B was detected predominantly in dendritic spines in prefrontal cortex and is enriched in cerebral cortex, caudatoputamen, hippocampal formation and cerebellum. But expression in most normal tissues is also clearly detected (Muly et al., 2004; Ouimet et al., 2004). PPP1R9B protein is downregulated in a great variety of human carcinomas but in a low percentage of tumors. Immunohistochemical analysis of PPP1R9B during cancer progression shows some correlation with tumoral progression and p53 mutations (Carnero, 2012).

Localisation

In most tissues, with higher levels in neural system.

Function

The structure of PPP1R9B suggests that functions as a protein scaffold that regulates both membrane and cytoskeletal functions. PPP1R9B performs important functions in the nervous system where it is implicated in the regulation of spine morphology and density, synaptic plasticity and neuronal migration. PPP1R9B could serve as a link between excitatory synapse transmission and changes in spine morphology and density (Allen et al., 2006; Hsieh-Wilson et al., 1999; Sarrouilhe et al., 2006).

PPP1R9B is a key modulator of the opiate action. PPP1R9B also promotes endocytosis of the mu-opioid receptor (Charlton et al., 2008). PPP1R9B has been implicated through PP1 binding in the regulation of AMPA-type glutamate receptor. PPP1R9B may serve to regulate excitatory synaptic transmission and plasticity by targeting PP1 to its cellular substrates, promoting their downregulation by dephosphorylation regulating the post-synaptic glutameric neurotransmission. PKA modulation of the localization of the PPP1R9B/PP1 complex could contribute to this effect. Plasticity in dendritic spines may underlie learning and memory, and observations in PPP1R9B null mice shown that PPP1R9B plays a role in learning in vivo (Hsieh-Wilson et al., 2003; Stafstrom-Davis et al., 2001; Yan et al., 1999).

PPP1R9B also has a role in the regulation of blood pressure and cardiac function (da Costa-Goncalves et al., 2008). Since PPP1R9B can control the intensity and duration of the G-protein receptor signaling influencing synaptic activity, PPP1R9B affects blood pressure through central mechanisms. In adult cardiomyocytes it has been proposed that PPP1R9B is an upstream regulator required for normal growth and excitation-contraction coupling, but is dispensable for β-adrenergic stimulation (Petzhold et al., 2011). Association of PPP1R9B with the α2-AR leads to alteration of α2-AR phosphorylation following agonist stimulation, suggesting that Spn acts mainly as an antagonist of arrestin. Thus, PPP1R9B participates in the regulation of signaling duration and sensitivity of the α2-AR response therefore regulating smooth muscle contraction. Following agonist treatment, PPP1R9B competition with GRK for α2-AR also prevents α2-AR endocytosis. Finally, a role for PPP1R9B in the formation of immunological synapses in dendritic cells has also been proposed, and PPP1R9B may be involved in the maintenance of cellular architecture by regulating actin assembly (Meng et al., 2009; Shaw and Filbert, 2009).

Implicated in

Various cancers

Prognosis

Expression levels decrease in some carcinomas.

Oncogenesis

PPP1R9B mRNA is lost in a percentage of renal carcinomas and lung adenocarcinomas (Carnero, 2012). More interestingly, analysis of normal vs tumoral samples of tumors of the CNS showed clear downregulation of PPP1R9B in tumoral samples. Furthermore, lower levels of PPP1R9B mRNA correlates with higher grade of ovarian carcinoma and chronic myelogenous leukaemia (Carnero, 2012). PPP1R9B is also lost in 20% and reduced in another 37% of human lung tumors (Molina-Pinelo et al., 2011). PPP1R9B reduction correlates with malignant grade and p53 mutations (Carnero, 2012).
The PPP1R9B gene is located in chromosome 17, at position 17q21.33, and in a cytogenetic area frequently associated with microsatellite instability and loss of heterozygosity.

This region is comprised of a relatively high density of tumor suppressor genes, including known (BRCA1, NME1), putative (JUP, prohibitin), and unidentified candidates distal to the BRCA1 locus (Carnero, 2012). Most of the studies on the 17q21 locus have focused on BRCA1, which exhibits a variable frequency in LOH depending on the type of tumor, stage and marker employed, and has been extensively studied in breast carcinomas (Caduff et al., 1999; Maitra et al., 1999; Querzoli et al., 2001). However, there are few studies that suggest the existence of unknown tumor suppressor genes for breast tumors in an area that includes the locus of PPP1R9B.

LOH in chromosome 17q21.3 has been observed in different tumors, including breast, ovarian, prostate, colorectal, gastric, renal and lung carcinomas, as well as in salivary gland carcinomas, an extremely aggressive neoplasm (Caduff et al., 1999; Maitra et al., 1999; Querzoli et al., 2001). The markers used in some of these studies with no linkage to BRCA1 point to NME1 as a tumor suppressor gene candidate to justify the functional impact of the allelic loss.

However, in different LOH studies an unidentified tumor suppressor gene nearby NME1 has been proposed. PPP1R9B is located in close proximity to NME1, at only 1 Mb, probably sharing the allelic loss in these studies.

The most relevant data according to PPP1R9B LOH came from a study on primary lung carcinoma (Abujian et al., 1998). This group performed an extensive LOH mapping in human lung cancers, using 15 highly polymorphic markers, 7 of which span 17q11-24 region. The higher LOH value appeared with the D17S588 marker, showing a 53% of loss. The D17S588 marker locates exactly within the PPP1R9B locus. These data provided the first robust data implicating PPP1R9B LOH in cancer. Closer tumor suppressor genes, such as BRCA1, were not seriously affected (6-13% LOH), nor other lung proliferative pathologies (squamous cell carcinoma and small cell carcinoma only showed minimal LOH, below 14%, for both PPP1R9B and BRCA1 markers).

Several genetic linkage studies using the marker D17S588 have suggested the existence of a tumor suppressor gene distal to BRCA1 (Porter et al., 1993; Porter et al., 1994). The maximum LOD scores obtained for D17S588 were of 5.44 in an Edinburgh study of 15 families (Cohen et al., 1993) and 21.68 in an analysis of 271 breast and breast-ovarian cancer families (Easton et al., 1993, Smith et al., 1993), indicating the importance of this locus in the pathology of cancer. The D17S588 marker lies inside the PPP1R9B gene.

Another study that investigated the correlation between p53 abnormalities and allelic loss of BRCA1, BRCA2 and adjacent loci in breast cancer found a strong correlation when using the D17S588 marker (Querzoli et al., 2001; Tseng et al., 1997). Again, PPP1R9B may be involved in the tumorigenic process by functioning, in association with a loss of p53 functionality, as a tumor suppressor (47.1% LOH) (Tseng et al., 1997).

**Learning and memory, regulation of blood pressure and cardiac function**

**Disease**

Learning and memory defects, problems in the regulation of blood pressure and cardiac function, tumors of different origin.
References


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