Atlas of Genetics and Cytogenetics in Oncology and Haematology

OPEN ACCESS JOURNAL

INIST-CNRS

Gene Section

Review

PTPN9 (protein tyrosine phosphatase, non-receptor type 9)

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Published in Atlas Database: November 2016
Online updated version : http://AtlasGeneticsOncology.org/Genes/PTPN9ID41922ch15q24.html
Printable original version : http://documents.irevues.inist.fr/bitstream/handle/2042/68528/11-2016-PTPN9ID41922ch15q24.pdf
DOI: 10.4267/2042/68528

Abstract

Review on PTPN9, with data on DNA, on the protein encoded, and where the gene is implicated.

Keywords: PTPN9; Endocytosis

Identity

Other names: PTPase-MEG2, PTPMEG2, MEG2

HGNC (Hugo): PTPN9

Location: 15q24.2

DNA/RNA

PTPN9 was originally cloned by screening libraries of the MEG-01 megakaryocyte leukemia cell line and of human umbilical vein endothelial cells (Gu 1992).

Description

The PTPN9 gene was mapped to chromosome 15q24.2 based on an alignment of the PTPN9 sequence (GenBank BC010863) with the genomic sequence (GRCh37).

Transcription

MEG2 mRNA detected in 12 cell lines gave an indication that the protein tyrosine phosphatase (PTP) is widely expressed.
A 4-kb RNA as analysed by Northern blot analysis was found in a variety of cell lines, indicating widespread expression of the gene (Gu 1992).

Protein

PTPN9 has a conserved PTP catalytic domain, and an NH2-terminal lipid-binding domain homologous to Sec14p, a yeast protein with phosphatidylinositol transferase activity, which is unique among PTPs (Gu 1992).
The N-terminal 254 amino acids are about 28% identical to cellular retinaldehyde binding protein-1 (RLBP1; 180090) and 24% identical to the yeast protein SEC14p.
The former is a carrier protein for 11-cis-retinaldehyde or 11-cis-retinol found in the retina and pineal gland, and the latter is a phosphatidylinositol transfer protein required for protein secretion from the Golgi apparatus.
The PTPN9 cDNA encodes a 593-amino acid protein that has no apparent signal or transmembrane domains but does include a C-terminal region with a catalytic domain that shows 30-40% identity with other PTPs (http://www.omim.org/entry/600768).

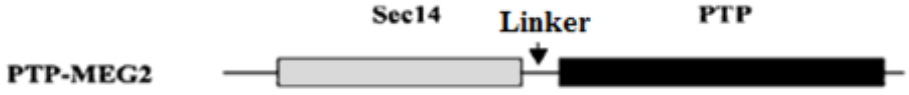

Figure 1. Schematic diagram of recombinant PTPN9 protein (Adapted from Zhao et al. 2003).The open and solid bars indicate SEC14 lipid-binding domain and PTP catalytic domain, respectively.

Description

PTPN9 is a 68-kDa, class I, cysteine-based, non-receptor PTP is widely expressed in many cell types including the brain and leukocytes (Gu 1992, Saito 2007). In these cells, most of the PTPN9 is located on the cytoplasmic face of secretory vesicles (Gjörloff-Wingren 2000, Wang 2002, Kruger 2002 and Huynh 2004). On the cytoplasmic face of the enclosing membrane of secretory vesicles, PTPN9 regulates vesicle size by promoting homotypic vesicle fusion through dephosphorylating NSF (N-ethylmaleimide-sensitive factor), a key regulator of vesicle fusion (Saito 2007). PTPN9 structural uniqueness among mammalian PTPs lies in the fact that it contains a domain in its N terminus with homology to yeast Sec14p, a phosphatidylinositol-binding protein (Sha 1998). This Sec14p homology (SEC14) domain of PTPN9 (Fig 1) is known to bind phosphoinositides (Kruger 2002, Huynh 2003, Krugmann 2002), a process that leads into enzymatic activation of the phosphatase domain (Kruger 2002, Huynh 2003). Using a series of deletion mutants, Saito et al identified the N-terminal SEC14 domain of PTPN9, residues 1-261, as the region containing the secretory vesicle targeting signal (Saito 2007). The SEC14 domain, alone or attached to a heterologous protein, was localized to intracellular vesicle membranes. In addition, two proteins, mannose 6-phosphate receptor-interacting protein PLIN3 (TIP47) and ARFIP2 Arfaptin2 altered PTPN9 localization when overexpressed, and elimination of TIP47 resulted in loss of PTPN9 function. It has been shown that the truncated form of the N-terminal SEC14 domain of PTPN9 has a significantly higher activity than the full-length enzyme (Qi 2002, Kruger 2002). By using lipid-membrane overlay and liposome binding assays, a specific binding of PTPN9 to phosphatidylserine was demonstrated (Zhao 2003). The binding was found to be mediated by the SEC14 domain. In intact cells, the SEC14 domain was found to play a prominent role in the localization of PTPN9 to the perinuclear region. Moreover, PTPN9 may play an important role through specific binding of phosphatidylserine, in regulating the signaling processes associated with phagocytosis of apoptotic cells (Zhao 2003).

Expression

The enzyme is expressed in many cell types (Gu 1992, Saito 2007), including at low levels in Jurkat T cells (Gjörloff-Wingren 2000), mast cells and lymphocytes (Wang 2002, Wang 2005).

Localisation

Reports have shown PTPN9 residence on internal membranes, including secretory vesicles and granules in neutrophils and lymphocytes where it regulates secretory vesicle size and fusion (Gjörloff-Wingren 2000, Wang 2002, Huynh 2003, Wang 2005). It is possible that once engulfed by phagocytes, a high level of phosphatidylserine in the outer membrane of apoptotic cells may alter the distribution of PTPN9 in phagocytes (Zhao 2003). It has been suggested that the physiological function of PTPN9 may be to regulate formation of secretory vesicles of a defined and cell type-specific size (Wang 2002). PTPN9 expression is higher in mast cells (granule size 400-600 nm) than in lymphocytes (granule size 200-300 nm) (Wang 2002).

Function

It was proposed that PTPN9 promotes homotypic fusion of immature secretory vesicles, which is a major step in the formation of these vesicles from post-Golgi transport vesicles containing cargo destined for secretion (Wang 2002, Huynh 2004, Huynh 2003, Wang 2005, Mustelin 2004). Additionally, PTPN9 may represent a novel connection between dephosphorylation of tyrosine and the regulation of secretory vesicles in hematopoietic cells (Wang 2002). Moreover, the possibility of PTPN9 expression in controlling the extent of the secretory apparatus of hematopoietic cells was proposed. Huyhn et al showed that PTPN9 regulates homotypic fusion of immature secretory vesicles by dephosphorylating the key regulator of vesicle fusion, N-ethylmaleimide-sensitive factor (NSF) (Huyhn 2004). PTPN9 can also regulate embryonic development (Wang 2005) and expansion of erythroid cells (Xu 2003). Studies have further demonstrated that PTPN9 controls insulin production, beta cell growth or insulin signaling by reducing insulin receptor (INSR) dephosphorylation in type II diabetes (Cho 2006, Chen 2010). Other studies have shown that PTPN9 promotes dephosphorylation of epidermal growth factor receptor (EGFR) and the receptor tyrosine protein kinase ERBB2, thereby impairing the activation of signal transducer and activator of transcription 3 (STAT3) (Yuan 2010) and STAT5 (Yuan 2010, Furth 2011) in breast cancer cells. From their observations, it was suggested that PTPN9-mediated modulation of secretory vesicle genesis and function plays an essential role in neural tube, vascular, and bone development as well as activation may participate in the transfer of hydrophobic ligands or may be involved in Golgi-related functions (Gu 1992). PTPN9 appears to regulate a balance by promoting fusion (anterograde transport) and reducing condensation (retrograde transport), thus increasing the size of secretory vesicles (Saito 2007). In addition, it was recently shown that the transport of neurotrophin receptor TRKA (NTRK1) to the cell surface requires PTPN9 activity (Zhang 2016). Trk A is a novel substrate of PTPN9 and is

dephosphorylated at both the kinase activation domain (Tyr674/675) and the signaling effector binding site (Tyr490). The studies were performed in neurite outgrowth and cortical neurons (Zhang 2016).

Implicated in

Breast cancer

ErbB family of the receptor protein-tyrosine kinase plays an important role in the progression of human cancers including breast cancer. Among the 43 human protein-tyrosine phosphatases analysed, Yuan 2010 discovered the knockdown of PTPN9 to significantly increase ERBB2 tyrosine phosphorylation in the SKBR3 breast cancer cell line. Additionally, knockdown of PTPN9 expression enhances tyrosine phosphorylation of the ErbB1/EGFR in the MDA-MB-231 breast cancer cell line. Their data suggested PTPN9 to be a negative regulator of breast cancer cells through targeting ErbB2 and EGFR and inhibiting STAT activation (Yuan 2010).

Hepatocellular carcinoma

PTPN9 expression was down-regulated in human hepatocellular carcinoma (HCC) tumor tissues, associate with worsened overall survival in HCC patients (Hu 2016). Depletion ofPTPN9 inhibits the apoptosis and promotes the proliferation of HCC cells.

Diabetes

PTPN9 have been identified as a modulator of insulin-dependent FOXO1 subcellular localization (Cho 2006). Ectopic expression of PTPN9 in cells to suppress insulin-induced phosphorylation of the insulin receptor, while RNAi-mediated reduction of PTPN9 transcript levels enhanced insulin action. Their findings implicated PTPN9 as a mediator of blood glucose homeostasis through antagonism of insulin signaling, and proposed modulation of PTPN9 activity to be an adequate strategy in type 2 diabetes treatment. Indeed, treatment with PTPN9 inhibitors can lead to enhanced insulin action both in vitro and in vivo (Zhang 2012).

Hematopoiesis

Xu et al identified PTPN9 to be contained in erythroid colony-forming cells (ECFCs) from polycythemia vera (PV), a human clonal myeloproliferative disorder (Xu 2003). Increased activity of PTPN9 in PV cells to be attributed to its elevated distribution in the membrane fraction. Additionally, the findings showed that PTPN9 plays a major role in the development of erythroid cells.

Immunodeficiency

PTPN9$^{-/-}$ mice were reported to be immunodeficient as they displayed severe developmental malformations, such as defective skull formation and intracranial bleeding (Wang 2005). The mice remained small and the majority of them died before birth or within the first neonatal days. Furthermore, they detected defective platelet activation and very little interleukin-2 secretion in these mice. They attributed all these abnormalities to defective PTPN9 secretion.

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This article should be referenced as such:

Nyesiga B, Gjörloff Wingren A. PTPN9 (protein tyrosine phosphatase, non-receptor type 9). Atlas Genet Cytogenet Oncol Haematol. 2017; 21(8):288-291.