

Gene Section

Review

PTPRR (protein tyrosine phosphatase, receptor type, R)

Mirthe Erkens, Hubertus Kremer, Rafael Pulido, Wiljan Hendriks

Department of Cell Biology, Nijmegen Centre for Molecular Life Sciences, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands (ME, WH), Department of Neurology, University Medical Center Groningen, The Netherlands (HK), IKERBASQUE, Basque Foundation for Science, Bilbao, Spain and BioCruces Health Research Institute, Barakaldo, Spain (RP)

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Abstract: Review on PTPRR, with data on DNA/RNA, on the protein encoded and where the gene is implicated.

Identity

Other names: EC-PTP, PCPTP1, PTP-SL, PTPBR7, PTPRQ

HGNC (Hugo): PTPRR

Location: 12q15

DNA/RNA

Description

Like its mouse ortholog (Chirivi et al., 2004), the human gene PTPRR represents a very complex locus as revealed by BLAST searches (Altschul et al., 1990) using the collection of deposited PTPRR cDNA query sequences (schematic diagram of PTPRR DNA/RNA).

Transcription

Differentially regulated promoters drive transcription from at least four different sites within the 285 kilobasepair-spanning genomic region and at five positions alternative splicing may occur.

Part of the resulting alternative transcripts make up the NCBI-annotated isoforms #1 through #5 in the nucleotide database (NM_002849, NM_130846, NM_001207015, NM_001207016 and NR_073474, respectively).

Furthermore, one of the alternative exons resides within a region that in the reverse transcriptional orientation is annotated as a fumarylacetoacetate hydrolase domain-containing protein 2 (FAHD2) pseudogene. Thus,

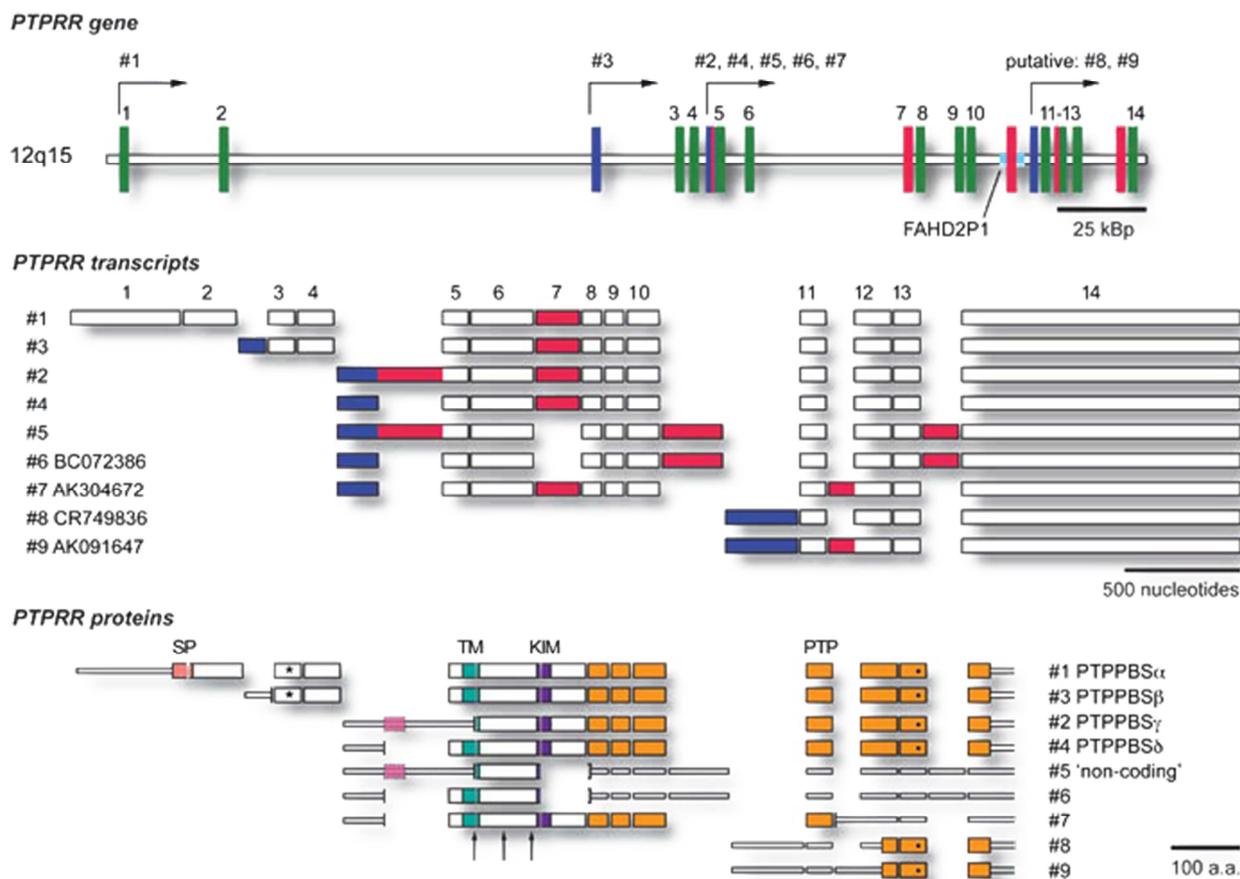
transcripts including this PTPRR exon - i.e. the isoform #5 types - carry FAHD2 antisense sequences that may have a regulatory impact on transcripts from the functional genes FAHD2A and FAHD2B that reside on chromosome 2q11.

Use of the most upstream promoter results in a ~4 kilobase-long transcript variant, isoform #1, encoding what Augustine and co-workers termed the human PTPPBSa isoform (Augustine et al., 2000).

This protein is equivalent to mouse PTPBR7, a canonical receptor-type transmembrane PTP. The human PTPPBSa transcript is built from sequences derived of 14 exons. This build-up was determined back in 2001 by Bektas and co-workers (Bektas et al., 2001) and recently confirmed and extended with isoform #2-specific exonic parts (Menigatti et al., 2009).

Within the distal region of the very large intron 2, a second alternative promoter is residing that leads to the human PTPPBSβ isoform (#3), which equals the mouse PTP-SL transcript. Although initially this variant was not encountered in human cDNA libraries (Augustine et al., 2000), the presence of four expressed sequence tags and two independent cDNA deposits (NM_001207015, AK295951) in public libraries underscore the existence of this transcript isoform in human tissue.

Then, within intron 4 - just proximal of exon 5 - a third alternative transcriptional start site is present that appears as the origin of the PTPPBSγ (#2) and PTPPBSδ (#4) variants (Augustine et al., 2000).



Schematic depiction of human gene PTPRR (upper panel), derived alternative transcripts (middle panel) and corresponding protein isoforms (lower panel). Arrows in the upper panel indicate the four distinct transcriptional start sites within the 285 kbp PTPRR locus on chromosome 12q15. Exon numbers according to transcript isoform #1 (acc.nr. NM_002849) are indicated above the corresponding, green boxes. Crimson boxes reflect the alternative first exons produced from the three distal promoters. Alternative spliced exonic parts are in dark-blue. The sky-blue area within intron 11 reflects the position of a pseudogene in the opposite transcriptional orientation. In the middle panel the build-up of the nine different PTPRR transcripts, deduced based on cDNA deposits in public databases, is depicted. The respective exon-derived sequence blocks are colour-coded as indicated above and are depicted unfused, to facilitate comparison with the gene build-up. See text for more details. The accession numbers for the major database entries defining the transcript variants #6 to #9 are given. The first five mRNAs correspond to annotated reference sequences (accession numbers are mentioned in the text). In the lower panel, again to facilitate comparison with gene and transcript build-up, the exon-encoded protein contributions are depicted unfused. Moreover, flanking the open reading frames (thick boxes) the non-coding mRNA parts are shown as thin white bars. The N-terminal, salmon protein domain reflects the signal peptide (SP). The transmembrane spanning region (TM) in PTPPBS α and PTPPBS β is shown in turquoise and the kinase-interacting motif (KIM) and protein tyrosine phosphatase catalytic domain (PTP) are coloured purple and orange, respectively. The asterisks indicate a conserved furin-like cleavage site and the black dot in the exon 13-derived amino acid sequence represents the essential catalytic site cysteine. A dashed pink box indicates the 30 aa open reading frame that is predicted based on database entry BX571751. Black arrows point to the position of methionines that may be functional as alternative starts upon PTPPBS γ / δ translation. Drawings are to scale (except for exon sizes in the top panel) and size bars are indicated.

Initially, it was thought that perhaps two different transcription start sites at close distance were used; an upstream one rendering isoform #4 and a second one, that would yield isoform #2, just some 200 base pairs downstream and within the part that is spliced out in transcript #4. However, multiple cDNA reads in the public database (most notably BX571751) disclose that transcription initiation of isoform #2 type mRNAs in fact occurs at the more upstream alternative promoter as well. Thus, in- or exclusion of a single sequence stretch just proximal of the canonical exon 5 appears the discriminating factor between isoforms #2 and #4. Mining the non-redundant nucleotide database did not provide entries that would back up the PBS γ and PBS δ

"+/-" additional alternatives that were suggested more than a decade ago (Augustine et al., 2000).

RNA variants represented by isoform #5 (acc. NR_073474) and database entry BC072386 also result from the use of the PBS γ / δ type promoter. These variants are unique, however, due to the splicing out of exon 7 and the inclusion of two alternative exons that reside in introns 10 and 13, respectively. Since exon 7 contributes 187 nucleotides, its exclusion alters the PTPRR reading frame and results in the incorporation of three exon 8-encoded missense amino acids followed by a premature stop. Thus, although isoform #5 is annotated as a noncoding RNA, truncated proteins that span the first 91 or 130 amino acids of PBS γ or

PBS δ , respectively, and then end with KYQ* may exist.

The above-discussed alternative exon within intron 10 is the one that overlaps with pseudogene FAHD2P1 that is annotated on the complementary strand. Perhaps due to remnants of transcriptional sequence elements that relate to the pseudogene, a bit more downstream in intron 11 there may be a potential promoter driving transcription of the last four PTPRR exons only.

Evidence for this comes from nucleotide database entries AK091647 (#9), AL711271 and most notably CR749836 (#8). The resulting transcript, with inclusion of a few hundred nucleotides contributing its poly-A tail, may well represent the ~3 kilobase-sized mRNA that has been detected in Northern blot analyses (Augustine et al., 2000). An open reading frame that constitutes the C-terminal 87 amino acids of the PTPRR PTP domain, hence representing an enzymatically inactive N-terminal truncation mutant, is discernible. It remains to be investigated whether the intron 11 transcription start is indeed genuine and whether the resulting RNAs have coding potential.

The cDNA in entry AK091647 (#9) yields one more surprise for the human PTPRR locus; 110 additional nucleotides directly upstream of exon 12 are retained within this clone. These additional bases were also found in AK304672 (#7), demonstrating that an alternative splice acceptor site for the exon 12 5' start exists.

Usually, the distal site is used and exon 12 donates 158 bases to the maturing transcript. In the cases just mentioned, the proximal site was used and the elongated exon 12 contributes 268 bases. If this occurs in transcripts originating from the upstream promoters, the PTPRR reading frame will dictate the addition of a single lysine to the protein before a stop codon is encountered. Hence, the resulting protein will lack the 121 C-terminal residues of the catalytic domain and will be enzymatically inactive. The predicted open reading frame within the transcripts dictated by the fourth, intron 11-residing promoter, however, is not altered by the exon 12 splice acceptor choice since the AUG start codon is contributed by the shared exon 12 part.

It is of note that directly downstream of PTPRR, in a head-to-tail fashion, yet another receptor-type PTP gene is located:

PTPRB. At first sight, the expression pattern in mouse brain is distinct from that of PTPRR (Lein et al., 2007; Hawrylycz et al., 2012) and future research will have to unveil whether both genes share transcriptional regulatory elements.

Pseudogene

There are no pseudogenes detectable for gene PTPRR in the human genome. Its closest relatives are the other two genes within the "R7" subclass of

classical PTPs (Andersen et al., 2001), PTPN5 and PTPN7, which encode for STEP and HePTP, respectively.

Protein

<i>Homo sapiens</i>	<i>Mus musculus</i>
PTPPBS α (#1)	PTPBR7
PTPPBS β (#3)	PTP-SL
PTPPBS γ (#2)*	PTPPBS γ -42
PTPPBS δ (#4)*	PTPPBS γ -37

PTPRR isoforms nomenclature. * Homology depending on the start codon used.

Description

From the above it is clear that human PTPRR encodes many different PTPRR protein isoforms. The longest one is a 657 single-pass transmembrane receptor-type PTP by virtue of its N-terminal signal peptide (SP).

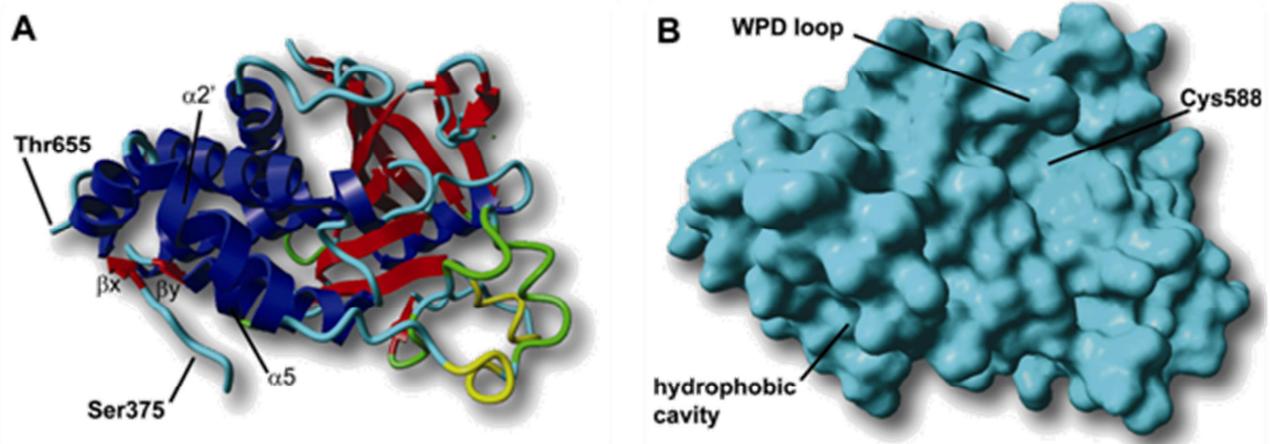
Removal of the SP from the precursor protein will yield a 71 kDa mature protein of the PTPBR7 type. This human PTPRR isoform #1 may additionally be post-translationally cleaved at an evolutionary conserved furin-like site, in analogy with the mouse ortholog (Dilaver et al., 2007), rendering a 59 kDa protein spanning 519 residues. This processing site is also present in the 545 amino acid long isoform #3 that has PTP-SL as its ortholog in mouse.

It may well be that it is actually the second AUG codon that is being used for the start of translation, as it was found in mouse (Chirivi et al., 2004). In that case, the PTPPBS β open reading frame would be 30 nucleotides shorter, and a 535 residue-spanning protein of 60 kDa would be synthesised.

Although isoform #3 lacks an obvious signal peptide preceding the transmembrane segment, one may expect that like PTP-SL (Noordman et al., 2008) it will behave as a type III transmembrane molecule (Spiess, 1995).

Human PTPRR transcript type #4 displays an open reading frame that predicts the synthesis of a 451 aa PTPRR isoform, coined PTPPBS δ (Augustine et al., 2000), that has a unique three amino acid N-terminus before it proceeds with the exon 5-encoded PTPRR read.

Consequently, this predicted 51 kDa protein contains the TM segment and may be topologically similar to the PTPPBS β protein isoform #3. The original PTPRR transcript #2 was thought to have its coding region starting exactly three nucleotides before exon 6-derived sequences, hence resulting in a 46 kDa cytosolic protein that spans 412 residues and is lacking any meaningful hydrophobic part.



Ribbon (A) and surface (B) type representation of the three-dimensional structure of the PTP domain in human PTPRR, as determined by X-ray crystallography (PDB code: 2A8B; (Eswaran et al., 2006)). Numbers are according to PTPPBS α protein isoform #1. Relevant structural elements, mentioned in the text, are indicated. The KIM domain and the $\alpha 0$ helix that was observed in the mouse PTPRR structure (PDB code: 1JLN) are N-terminal of Ser375 and were absent in the human recombinant protein part used for crystallization. Blue parts represent alpha helices and red domains symbolize beta strands. Yellow portions indicate 3_{10} helices and the green parts represent random coil segments. Molecular graphics was created with YASARA (Krieger et al., 2002).

Multiple cDNAs now argue in favour of extending the 5' end of the type #2 transcript and by doing so the (more) full-length cDNA then only displays a rather short, 30 aa protein-encoding ORF due to a stop codon in the part that is spliced out in isoform #4-type transcripts.

Adding to the complexity is that in mouse PTPPBS γ mRNA it is not the first but rather the second and third AUG codon that is used by the translational machinery (Chirivi et al., 2004). If the same holds true in human, then the PTPPBS γ/δ -type transcripts would yield 42 and 37 kDa sized cytosolic PTPs independent of the in- or exclusion of the 283 nucleotide intron preceding exon 5.

There are two domains that are present in all PTPRR proteins encoded by transcript isoforms #1 through #4; a so-called kinase interaction motif (KIM (Pulido et al., 1998)) and, of course, the catalytic PTP domain. This classical, strictly phosphotyrosine-specific catalytic PTP segment spans some 280 conserved amino acids and includes the active site cysteine that is essential for the nucleophile attack on the phosphorus of the phosphotyrosine in the substrate protein (Guan and Dixon, 1991). Overall, the three-dimensional structure of PTP domains shows only minor differences in the core elements. For instance, the structure of the catalytic segment in the "R7" PTP subfamily (that is comprised of PTPRR, STEP and HePTP (Andersen et al., 2001)) displays a short β sheet consisting of the N-terminal βx and C-terminal βy strands (Eswaran et al., 2006) that is not encountered in the founding PTP1B structure (Barford et al., 1994). Also, this R7-type PTP domain structure contains several helices (Szedlacsek et al., 2001; Mustelin et al., 2005; Eswaran et al., 2006) that are additional to the canonical structure in other PTPs (Barr et al., 2009). Most notably, PTPRR, STEP and HePTP have an additional N-terminal helix

(termed " $\alpha 0$ ") that is stabilized by hydrophobic interactions with helix $\alpha 5$ and the loop following helix $\alpha 2'$ (Szedlacsek et al., 2001; Mustelin et al., 2005; Eswaran et al., 2006). This results in a hydrophobic cavity of $\sim 16\text{\AA}$ depth that may be instrumental in the regulation of enzyme activity and substrate specificity (Szedlacsek et al., 2001). Helix $\alpha 0$ is located 15 residues downstream of the KIM motif, a 16 amino acid sequence that is essential for PTPRR's interaction with the MAP kinases ERK1, ERK2, ERK5 and p38 (Pulido et al., 1998; Zúñiga et al., 1999; Buschbeck et al., 2002; Muñoz et al., 2003). Thus, helix $\alpha 0$ may facilitate proper positioning of the KIM to ensue interactions with the docking groove in MAP kinases (Tárrega et al., 2005). As a consequence not only the regulatory tyrosine in the MAP kinase's activation loop is dephosphorylated, causing its inactivation (Pulido et al., 1998), but additionally the physical interaction prevents MAP kinase translocation to the nucleus (Blanco-Aparicio et al., 1999; Zúñiga et al., 1999). Vice versa, the association of a KIM-containing PTP with an active MAP kinase triggers specific phosphorylation of a threonine residue within the PTP's $\alpha 0$ helix (Pulido et al., 1998; Muñoz et al., 2003). The consequence of this phosphorylation event, however, remains to be investigated. Quite opposite, the effect of protein kinase A (PKA)-mediated phosphorylation of a conserved serine residue within the KIM motif is well studied since it abolishes the binding and subsequent dephosphorylation of MAP kinases by KIM-containing PTPs (Blanco-Aparicio et al., 1999; Saxena et al., 1999; Nika et al., 2004).

The predicted proteins that may result from translation of the PTPRR messenger types #5 through #9 will be enzymatically dead. The transcript #5 and #6 derived types will lack all PTP domain residues and also the KIM segment is far from complete, all due to a reading

frame change that is caused by exon 7 skipping. Depending on the AUG choice, a small protein that would contain the TM domain might be produced, which could theoretically influence the multimerization behaviour of the PTPBR7 and PTP-SL type isoforms (Noordman et al., 2008). PTPRR splice forms that manage to maintain the long version of exon 12 (e.g. the #7 type), however, will produce protein variants that only lack the C-terminal 121 amino acids. Such truncated, KIM-containing proteins would be enzymatically inactive but may compete with endogenous full-length PTPRR isoforms for binding to MAP kinases or other PTPRR-associating biomolecules. Any regulatory impact of the hypothetical 87 amino acid long protein that corresponds to the ORF in transcript versions #8 and #9 would be purely speculative.

Expression

Isoform-specific expression studies on human samples are limited to RT-PCR analyses (Augustine et al., 2000) which in general point to expression patterns that are quite similar to mouse (Van Den Maagdenberg et al., 1999; Augustine et al., 2000) and rat (Watanabe et al., 1998). Human PTPBR7 is expressed exclusively in brain and the PTPBR7 γ/δ -type transcripts are also detectable in various other tissues, most notably uterus and intestine (Augustine et al., 2000). PTPBR7 β isoform expression was not addressed in that study. Given that both in mouse and in rat a developmental promoter switch occurs in cerebellar Purkinje cells (PCs), favouring PTP-SL-type expression in mature PCs, it seems likely that also in human cerebellum the promoter within PTPRR intron-2 will drive postnatal expression of PTPBR7 β isoforms. The notion that PTPBR7 γ/δ -type isoforms are detectable outside brain is of importance for recent studies that implicate PTPRR in carcinogenic processes in cervix and colon (Menigatti et al., 2009; Su et al., 2013).

Localisation

No detailed studies on the subcellular localization of human PTPRR protein isoforms have been performed and, again, only inference from mouse and rat data (Shiozuka et al., 1995; Ogata et al., 1999; Van Den Maagdenberg et al., 1999; Dilaver et al., 2003; Noordman et al., 2006; Noordman et al., 2008; Hendriks et al., 2009) remains. Based on this, it seems reasonable to postulate that isoform #1 will display a PTPBR7-like cell surface expression and that isoform #3 may reside on the trans-Golgi network and multivesicular bodies or sorting endosomes, like mouse PTP-SL does. Depending on the translational start site choice, the other isoforms produce either PTP-SL-like vesicle-associated versions or, more likely, cytosolic proteins that resemble murine PTPBR7 γ . Intriguingly, the mouse transmembrane PTPRR isoforms form multimeric complexes and their relative PTP activity is significantly lower than that of the cytosolic PTPBR7 γ

(Noordman et al., 2008). This predicts regulatory potential for any biomolecule that would bind to the PTPBR7 and/or PTP-SL parts that are N-terminal of the transmembrane segment. Identification of receptor-type PTP ligands is a cumbersome process (Stoker, 2005; Mohebaniy et al., 2013) and although mouse PTPBR7 extracellular domain displayed a clear affinity for highly myelinated brain regions (Chesini et al., 2011) the corresponding PTPRR ligands still await proper identification.

Function

The localization of the two transmembrane mouse PTPRR isoforms on anterograde as well as retrograde endocytic vesicles (Hendriks et al., 2009) suggests either a role in the regulation of vesicle transport or a fate as cargo in these compartments. In line with the first option, protein interaction and transfection studies pointed at a potential functional interaction with β 4-adaptin, an AP-4 complex subunit that participates in vesicle sorting (Dilaver et al., 2003). Further studies are needed to corroborate this finding and it remains to be established whether this holds for human PTPRR as well. On the contrary, ample evidence now supports a regulatory impact for PTPRR isoforms on MAP kinase signaling. After the initial ectopic overexpression experiments that disclosed the KIM-dependent and PKA-regulated PTPRR-MAP kinase interactions (Pulido et al., 1998; Blanco-Aparicio et al., 1999; Ogata et al., 1999) it was surprising to find that endogenous PTPRR apparently was dispensable for proper EGF- and NGF-induced MAP kinase activity in rat PC12 cells (Noordman et al., 2008). Findings in PTPN7 deficient mice, however, had suggested that KIM-containing PTP impact on MAP kinase cascades might be very subtle (Gronda et al., 2001). Furthermore, pharmacological inhibition (Paul et al., 2003; Valjent et al., 2005) and mouse knock-out studies also proved PTPN5 to be a physiological regulator of MAP kinase cascades (Venkitaramani et al., 2009). Indeed, also Ptprr knock-out mice displayed MAP kinase hyperphosphorylation in relevant tissues (Chirivi et al., 2007).

PTPRR's closest homolog, the PTPN5-encoded protein STEP, is additionally capable of dephosphorylating the cytosolic tyrosine kinase Fyn, Pyk2, and subunits of AMPA and NMDA receptors in neuronal cells, implicating KIM-containing PTPs in neuronal functions like synaptic transmission (Baum et al., 2010; Xu et al., 2012a). There is even evidence that PTPN5 is linked to the pathophysiology of diverse neuropsychiatric disorders in man, including Schizophrenia and Alzheimer's disease (Goebel-Goody et al., 2012; Xu et al., 2012b). Although direct evidence for an impact of PTPRR on Src-family kinase or AMPA and NMDA receptor subunit phosphorylation levels has not yet been obtained, it remains an interesting possibility in view of the phenotypic consequences of PTPRR deficiency in mice (Chirivi et

al., 2007) and the proposed links with some human (neuro)pathological conditions (below).

Implicated in

inv(12)(p13q15) in acute myelogenous leukemia

Note

An *inv(12)(p13q15)* translocation detected in an acute myelogenous leukemia was found to result in multiple fusion transcripts spanning the first three or four exons of gene TEL in combination with the final five to eight exons of PTPRR (Nakamura et al., 2005). Only a single chimeric TEL/PTPRR fusion transcript, however, dictates an open reading frame that would be in-frame with PTPRR sequences. This fusion transcript joins the fourth TEL exon with the ninth of PTPRR and results in a protein that lacks the first (exon 8-encoded) thirty-odd residues of the PTP catalytic domain and thus will be enzymatically inactive. It therefore seems more likely that an altered functionality of the TEL transcriptional repressor part in the chimeric protein is instrumental in the disease.

Colorectal and cervical cancers

Note

Recent findings, however, more directly support a role for PTPRR in cancer etiology. RNA expression studies in mice highlighted PTPRR isoform expression in the epithelial linings of the intestine (Augustine et al., 2000). Gene expression profile analyses revealed that PTPRR transcription was markedly downregulated in colorectal tumors as compared to normal mucosa (Sabates-Bellver et al., 2007). The decreased expression in precancerous and cancerous colorectal tumors resulted from epigenetic changes, both at the level of CpG island DNA methylation and histone-tail modification, that were also observed in colon cancer cell lines and were maintained in metastases (Menigatti et al., 2009). The finding was recently confirmed in an independent study on colon carcinomas (Laczmanska et al., 2013) and can now be extended to cervix cancer on the basis of a study that concentrated on the consequences of DNA methyltransferase 3B (DNMT3B) hyperactivity in invasive cervical cancer (Su et al., 2013). It turned out that PTPRR was silenced through DNMT3B-mediated methylation. Given the impact of the RAS/RAF/MAPK signalling axis in cancer cell proliferation, it is not difficult to envision that PTPRR down-regulation would aid constitutive activation of this key pathway. Furthermore, PTPRR re-expression was shown to inhibit the expression of the oncogenic human papillomavirus E6/E7 proteins (Su et al., 2013), providing yet another advantage for HPV-positive cells to downregulate this PTP gene. PTPRR is normally not only expressed in the cervix but also in endometrial tissue. By comparing mRNA levels

throughout the menstrual cycle, PTPRR was found to be increased some fifty-fold from the proliferative to the secretory phase in endometrial tissue (Sherwin et al., 2008). Furthermore, PTPRR expression appeared an additional four-fold higher in late secretory phase tissue of women with endometriosis as compared to controls, which suggests that PTPRR may prevent normal endometrial differentiation and could represent a predisposing factor in the aetiology of endometriosis (Sherwin et al., 2008).

Type 2 diabetes

Note

The mapping of a novel type 2 diabetes susceptibility locus on chromosome location 12q15, back in the former century, early on triggered the testing of PTPRR as a candidate risk gene. Although the subsequent study provided a first snapshot of the gene and also yielded multiple polymorphisms, none of the identified mutations did segregate with diabetes (Bektas et al., 2001). Thus PTPRR is excluded as a risk gene at the type 2 diabetes locus on chromosome 12q15.

Psychoneuropathologies

Note

In prefrontal cortex and hippocampal areas in brains of depressed suicide subjects a significant reduction of MAP kinase transcript levels and increased amounts of a dual-specificity MAP kinase phosphatase have been noted (Dwivedi et al., 2001). Intriguingly, transcriptome-wide micro-array expression studies on postmortem orbitofrontal cortex tissue from violent suicide victims subsequently revealed a 1.5-fold upregulation of PTPRR mRNA levels when compared to controls (Thalmeier et al., 2008). This suggests a picture in which the reduction of MAP kinase signals in distinct brain areas - for example due to PTPRR aberrancies - may ultimately lead to profound mood distortions with eventual violent or deadly consequences. Such mood disorders are quite hard to study in mouse models and also the subtleties in brain expression patterns will severely hamper reductionistic studies on the psychopathophysiological relevance of these findings.

Recently, however, an additional correlative finding aids in building a case for involvement of PTPRR in psychoneuropathologies. It is currently well accepted that genetic components are contributing to major depressive disorder (MDD), a chronic and rather common mental disease. Given that reduced MAP kinase activity has been noted in MDD pathogenesis (Einat et al., 2003; Chen et al., 2006) and that PTPRR proteins inhibit this signaling pathway, it made sense to test whether PTPRR perhaps represents an MDD risk gene. By monitoring the distribution of 16 single nucleotide polymorphisms (SNPs) at the PTPRR locus in a Chinese Han population indeed one (rs1513105) demonstrated allelic association with an increased risk for MDD, but primarily in the female subjects (Shi et

al., 2012). Replication in additional cohorts will be the next step.

Like for MDD, the heterogeneous etiology of alcohol use disorders (AUD) predicts a complex interplay of environmental and heritable factors and the latter may include impaired MAP kinase signaling circuits. By combining genome wide association studies (GWAS) and gene set enrichment analyses (GSEA) on subjects characterized for alcohol response level phenotypes, a set of 173 genes that appear relevant for the disorder, among which PTPRR, could be extracted (Joslyn et al., 2010). Several had a reported involvement in alcohol response and addiction, and a specific enrichment for neuronal signaling genes - especially the ones impacting on glutamate signaling - was apparent (Joslyn et al., 2010). Analogous to STEP (Baum et al., 2010), PTPRR may modulate AMPA and NMDA receptor levels and as such is an appealing genetic component for the modulation of alcohol's effects.

Myopia

Note

The most recent addition to the list of disease associations for PTPRR is that of nearsightedness, or myopia (Hawthorne et al., 2013). For this common ocular genetic disease over 20 candidate genomic loci have been put forward, including one on chromosome 12q21-23 that links to high-grade myopia. Subsequent genetic association studies using hundreds of SNPs within the linkage region yielded several that significantly associated with the disease, including rs3803036 that represents a Lys>Arg missense mutation in PTPRR (Hawthorne et al., 2013). Microarray analyses revealed that PTPRR is differentially expressed in fetal and adult ocular tissue, warranting further studies on its role in myopic development.

To be noted

Note

Ptpr knock-out mice display mild, ataxia-like, locomotive impairment (Chirivi et al., 2007) but the gene's location in human does not match with the various ataxia loci that have been mapped thus far and that still await identification of the underlying gene defects (Espinós et al., 2009).

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