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Cloning, expression and chromosomal localization of a new putative receptor-like protein tyrosine phosphatase*

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We have isolated a mouse cDNA of 5.7 kb, encoding a new member of the family of receptor-like protein tyrosine phosphatases, termed mRPTPμ. The cDNA predicts a protein of 1432 amino acids (not including signal peptide) with a calculated M_r of 161 636. In addition, we have cloned the human homologue, hRPTPμ, which shows 98.7% amino acid identity to mRPTPμ. The predicted mRPTPμ protein consists of a 722 amino acid extracellular region, containing 13 potential *N*-glycosylation sites, a single transmembrane domain and a 688 amino acid intracellular part containing 2 tandem repeats homologous to the catalytic domains of other tyrosine phosphatases. The N-terminal extracellular part contains a region of about 170 amino acids with no sequence similarities to known proteins, followed by one Ig-like domain and 4 fibronectin type III-like domains. The intracellular part is unique in that the region between the transmembrane domain and the first catalytic domain is about twice as large as in other receptor-like protein tyrosine phosphatases. RNA blot analysis reveals a single transcript, that is most abundant in lung and present in much lower amounts in brain and heart. Transfection of the mRPTPμ cDNA into COS cells results in the synthesis of a protein with an apparent M_r of 195 000, as detected in immunoblots using an antipeptide antibody. The human RPTPμ gene is localized on chromosome 18pter-q11, a region with frequent abnormalities implicated in human cancer.

Receptor-like tyrosine phosphatase

1. INTRODUCTION

Reversible protein phosphorylation has long been considered a key mechanism for regulating cellular processes [1]. While the majority of protein phosphorylation occurs at serine and threonine residues, phosphorylation at tyrosine residues is attracting a great deal of interest since the discovery that many oncogene products and growth factor receptors posses intrinsic protein tyrosine kinase (PTK) activity. The importance of tyrosine phosphorylation in growth factor signal transduction, cell cycle progression and neoplastic transformation is now well established [2–5]. Tyrosine phosphorylated proteins can be specifically dephosphorylated through the action of protein tyrosine phosphatases (PTPs) [6–9]. Such PTPs are likely to have an equally important role as PTKs in the control of cellular growth and differentiation and could conceivably be the products of tumor suppressor genes. The rapidly growing family of PTPs can be classified into 2 subgroups : (i) cytosolic proteins, in particular PTP1B [10–14] and the T-cell PTP [15], and (ii) transmembrane proteins that have structural hallmarks of receptors for extracellular signals. Receptor-like PTPs (RPTPs) consist of a cytoplasmic catalytic region, a single transmembrane segment and a putative ligand-binding extracellular domain. To date, various cDNAs for RPTPs have been isolated, notably for LCA (leukocyte common antigen) or CD45 [16], LAR [17], PTPα,β,ε [18–23] and several partial cDNA sequences for putative RPTPs, termed PTPγ,δ, and ζ [18,20]. PTPs appear to be conserved during evolution, since homologous cDNAs have been isolated from *Drosophila* [24], yeast [25], *Caenorhabditis elegans* and *Styela plicata* [26].

Although none of the putative ligands for the RPTPs have yet been identified, it is widely assumed that RPTPs may play a key role in signal transduction and growth control. Recent studies with the leukocyte specific RPTP, CD45, provide direct support for that view [27].

In view of the potential importance of PTPs in normal and malignant growth, we have used PCR to isolate cDNAs encoding new members of the PTP family, as a first step in exploring their biochemical and biological functions. We report here the molecular cloning of a

*The sequences reported in this paper have been deposited in the EMBL/ GenBank data base under the accession numbers X58287 (mRPTPμ), X58288 (hRPTPμ) and X58289 (mRPTPβ).

Abbreviations: PTP, protein tyrosine phosphatase; RPTP, receptor-like protein tyrosine phosphatase; PTK, protein tyrosine kinase; FN, fibronectin; PCR, polymerase chain reaction; LAR, leukocyte common antigen-related molecule.

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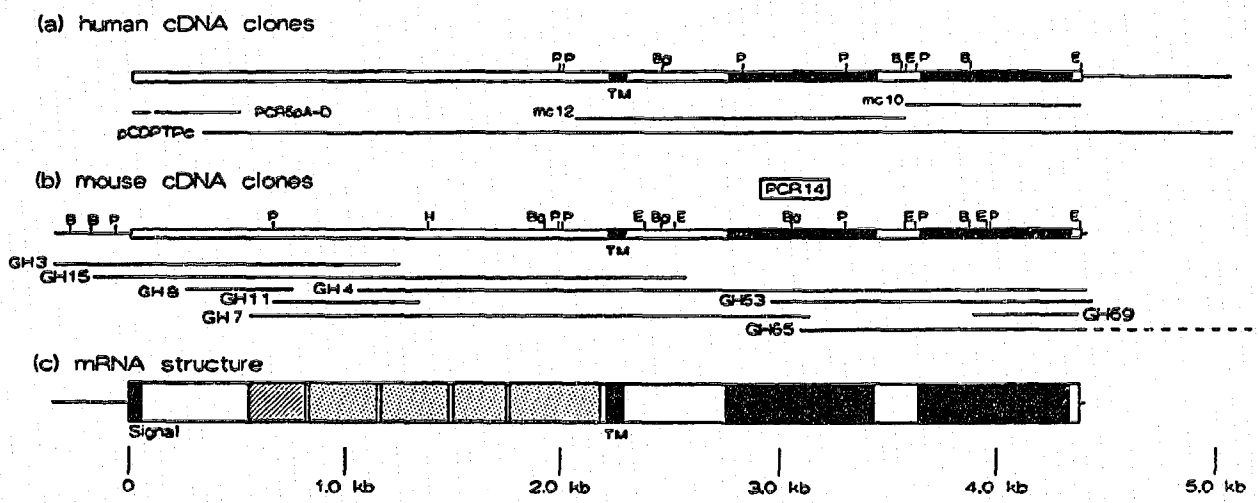

Fig. 1. (A and B) Restriction maps of overlapping human RPTPμ cDNA clones (A) and mouse RPTPμ cDNA clones (B). The open reading frame is shown as a box. Solid lines indicate the size and order of the various cDNA clones. The broken line indicates the 3'-end containing a poly-A tail, found only in one clone (GH65), which has not been sequenced completely. Restriction sites are : *Pst*I (P), *Hin*dIII (H), *Bgl*II (Bg), *Bam*HI (B), and *Eco*RI (E). (C) Model of the mRNA structure of the mRPTPμ. Thin lines indicate 5' and 3' untranslated regions. Black boxes indicate the putative signal peptide, transmembrane segment and both catalytic PTP domains. The hatched regions indicate the Ig-like domain and the stippled regions indicate FN type III-like domains.

new mouse RPTP, designated mRPTPμ, encoding a transmembrane protein of 1432 amino acids, whose extracellular domain shares some structural motifs with LAR. In contrast to LAR, however, mRPTPμ shows a limited tissue distribution, with highest expression in lung. In addition, we have cloned the human homologue of RPTPμ and localized the gene on human chromosome 18.

2. MATERIALS AND METHODS

2.1. *Materials and General Methods*

Restriction endonucleases and modifying enzymes were purchased from Boehringer Mannheim, New England Biolabs, Promega and Stratagene. Recombinant Thermus aquaticus (*Taq*) polymerase was from Perkin-Elmer Cetus. Oligonucleotide primers were synthesized on a New Brunswick Biosearch DNA synthesizer. Standard DNA manipulations and cloning procedures were done according to Sambrook et al. [28]. DNA probes were labeled with [α-^{32}P]dATP (Amersham), using random primed oligonucleotides as primer [29](Boehringer Mannheim kit).

2.2. *Isolation of RNA and Northern analysis*

Total RNA was prepared from mouse tissues by the guanidinium thiocyanate/CsCl procedure [30]. Total RNA was electrophoresed in a 1% agarose gel containing formaldehyde [31] and transferred to Hybond N membranes [32]. Baked filters were hybridized at 42°C with a ^{32}P-labeled DNA probe (5' *Pst*I-fragment bp 658–1985) for 20 h as described [33].

2.3. *Polymerase Chain Reaction and Subcloning of PTP Domains*

Total RNA from mouse brain was converted to single stranded cDNA by oligo(dT) priming and AMV reverse transcriptase. This cDNA was used as a template for in vitro amplification with *Taq* DNA polymerase and degenerate primers A (5'-GCGTGAATTCTA^{C}/$_{T}$AT^{C}/T/$_{A}$GCIACICA^{G}/$_{A}$GGICC-3') and B (5'-GGTCGAATTCG-GIACICC^{G}/$_{A}$TG^{G}/$_{A}$TCIGGCCA-3'). The PCR was carried out in a Perkin-Elmer Cetus thermo-cycler using 30 cycles. The cycles were: 1 min at 94°C (denaturation), 2 min at 50°C (annealing) and 2 min at 72°C (extension). Fragments of 300 bp were isolated from a low-melting-point agarose gel, digested with *Eco*RI, subcloned in PGEM-3-Zf(−) (Promega) and sequenced.

2.4. *Isolation of RPTPμ cDNA Clones*

A human λgt11 mammary carcinoma cDNA library (Clontech) was screened using standard protocols [28] with the purified insert of PCR clone14 as probe. cDNA inserts from purified plaques were subcloned into PGEM-3-Zf(−) (Promega) and sequenced. The insert of clone mc12 was used to screen a pCD plasmid Hela cDNA library (kindly provided by S. Hanks [34]). A random-primed λZAPII mouse lung cDNA library (Stratagene) was screened under reduced stringency conditions using the insert of clone pCDPTPc as a probe. High and low stringency hybridizations were done under the same conditions except for incubation temperatures (hybridization at 42°C or 32°C and washings at 65°C or 45°C, respectively). To clone the 5' coding sequence of human RPTPμ by PCR, using first strand cDNA prepared from total Hela RNA, we used 2 oligonucleotides (5'-GGG-GATCCATGAGGACACTTGGGACTTG-3', bp −2–20 and 5'-GC-GGGATCCTTCACCTCATCGATAGCG-3', bp 529–510)

2.5. *Nucleotide Sequencing*

DNA sequence determination was performed using the Pharmacia T7 sequencing kit. To obtain the complete sequence on both strands, nested deletion mutants were generated using the Erase-a-base kit (Promega) and/or synthetic oligonucleotide primers specific for RPTPμ. Sequence data were analyzed using GCG software [35].

2.6. *Expression of the RPTPμ Protein*

A full-length mouse RPTPμ cDNA was constructed by cloning a *Hin*dIII DNA fragment (bp −160–1372) from clone GH15 (containing the 5' end, Fig. 1b) into the unique *Hin*dIII site (1372) of clone GH4 (containing the 3' end, Fig 1b). This cDNA was then released as one fragment using the *Sal*I and *Xba*I sites in the polylinker and cloned into the eukaryotic expression vector pMT2m, resulting in plasmid pMT2mFL1. pMT2m was constructed by introducing a polylinker using 2 oligonucleotides (5'-AATTCTCTAGACTCGAGGTACCG-CGGCCGCCCGGGTCGACCTGCA-3' and 5'-GGTCGACCCGG-

GCGGCCGCGGTACCTCGAGTCTAGAG-3') between the *Pst*I and the *Eco*RI restriction site of the pMT2 vector [28].

A truncated cDNA encoding only the intracellular domain of hRPTPμ was generated as follows. An oligonucleotide (5'- GCGCTC-GAGCCGCCACCATGTTGAAGAAGAGGAAACTG-3') containing a *Xho*I restriction site, a start codon, a Kozak consensus sequence and bases 2293–2309 of hRPTPμ was used together with oligonucleotide 1330 (5'-CTTAGCCGAGTCCCATGG-3', bp 2757–2740) to amplify 487 bp of the intracellular domain in a PCR with clone mc12 as template. The amplified product was digested with *Bgl*II and *Xho*I and together with a *Bgl*II-*Xho*I fragment (bp 2449–4871) cloned into a Bluescript KS vector (Stratagene). A *Xho*I fragment of this plasmid, containing the intracellular part of human RPTPμ was then subsequently recloned into the pMT2 expression vector resulting in plasmid pMT2TR. pMT2TR and pMT2mFL1 were transfected into COS-7 cells as described [36].

2.7. *Antibody Preparation*

Rabbits were injected with a synthetic peptide corresponding to the predicted C-terminus of the RPTPμ protein (residues 1436–1452) coupled to bovine serum albumin using the cross-linking agent EDAC (1-ethyl-3-(3-dimethyl-aminopropyl) carbodiimide). Two subsequent booster injections were given at 2-week intervals with the peptide coupled to keyhole lympet hemocyanine. The antiserum was named Ab37.

2.8. *Immunoblotting*

Cos-7 cells were cultured in 10 cm plates. Two days after transfection cells were washed once with PBS (PBS: 137 mM NaCl, 3 mM KCl, 8.1 mM Na_2PO_4, 1.5 mM KH_2PO_4), lysed in 4×SDS sample buffer (250 mM Tris pH 6.8, 8% SDS, 10% v/v glycerol, 100 mM DTT, 0.01% w/v Bromophenol blue) and boiled for 5 min. One-tenth of the samples was put on 7.5% SDS-PAGE gel. After electrophoresis, proteins were transferred to nitrocellulose. Nitrocellulose filters were blocked with 5% milk powder (Nutricia) in TBST (TBST: 10 mM Tris pH 8.0, 1.5 mM NaCl, 0.05% Tween-20, 0.01% BSA). Blots were probed with 1 to 1000 diluted anti-serum and developed using alkaline phosphatase as described [33].

2.9. *Chromosomal Localization of the hRPTPμ Gene*

For our chromosomal localization studies a panel of well defined human–rodent somatic cell hybrids was used [37]. These hybrid lines were isolated after fusion of human cells, obtained from different donors, with hypoxanthine phosphoribosyl-transferase- or thymidine kinase-deficient rodent cells. Parental and hybrid cells were grown in F10 or RPMI 1640 medium supplemented with 2 mM glutamine, 100 U/ml penicillin, 100 μg/ml streptomycin and 10% fetal calf serum. For the chromosomal analysis of the hybrid cell lines air-dried chromosome spreads were made according to standard procedures [37]. Of each cell line at least 16 metaphases were examined using R banding after heat denaturation. The cells used for chromosomal analysis and DNA extraction were always derived from the same culture batch.

3. RESULTS

3.1. *New Members of the Protein Tyrosine Phosphatase (PTP) Family Identified by PCR*

In an attempt to identify new members of the PTP gene family, we used the following PCR-based protocol. Degenerate oligonucleotides were designed corresponding to conserved regions (amino acids YIA$^{A}/_{T}$QGP and WPDHGVP) of PTP catalytic domains [38,39]. A first round of 30 PCR-cycles was carried out on first strand cDNA synthesized from mouse brain RNA. A sample (1/50) of this first reaction was reamplified for 25 cycles with the same oligonucleotides. The major product of this second PCR was a fragment of the expected size of 300 bp (not shown). Sequence analysis revealed the presence of different PTP clones including both catalytic domains of LAR, the catalytic domain of the T-cell PTP, and two new members of the family, one of which appeared to be the putative mouse homologue* of HPTPβ [18]. The other member (clone PCR14, Fig. 1), termed RPTPμ, showed similarities but was not identical to previously cloned PTPs.

3.2. *Isolation of RPTPμ cDNA Clones*

The 300 basepair insert of clone PCR14 (bp 2902–3200 in the final sequence, Fig. 2) was used to isolate two cDNA clones (mc10 and mc12, Fig. 1a) from a human mammary carcinoma library. One additional human cDNA clone (pCDPTPc in Fig. 1a) of 4.7 kb was isolated from a Hela cDNA library. Sequence analysis showed that clone pCDPTPc lacked the 5' end. In an effort to obtain a complete RPTPμ cDNA, we used the entire insert of clone pCDPTPc to screen a mouse lung cDNA library. Several overlapping clones were isolated (Fig. 1b) spanning a stretch of approximately 5.7 kb closely corresponding to the size of the mRNA as detected in Northern blot analysis (Fig. 5 ; discussed below). The 5' coding sequence of human RPTPμ was cloned (clones PCR5'A–D) from human cDNA by PCR using a primer, starting at the ATG codon, based on the corresponding mouse sequence.

3.3. *Analysis of Mouse RPTPμ cDNA Clones*

The cDNA sequence and the deduced amino acid sequence of mRPTPμ are depicted in Fig. 2. The nucleotide sequence contains a 356 bp 5' untranslated leader, a single open reading frame of 4356 bp encoding a polypeptide of 1452 amino acids and a 3' untranslated region. The putative ATG/methionine start codon at position 1 agrees well with the described criteria for the initiation of translation [40]. The deduced amino acid sequence shows typical features of a type I transmembrane glycoprotein. The N-terminal 20 residues have all of the features of a typical signal peptide [41]. The most likely cleavage site is between residues 20 and 21. Hence, the mature protein contains 1432 amino acids with a predicted mass of 161 636. A single transmembrane-spanning α-helical segment of 22 hydrophobic residues is predicted at amino acids positions 743–764. The putative transmembrane domain is followed by a sequence of mostly basic residues as is common to the cytoplasmic face of transmembrane domains of many proteins. There are 13 potential sites for *N*-linked glycosylation in the extracellular domain (underlined in Fig. 2). The predicted intracellular region contains 2 tandemly repeated domains with significant similarity to the catalytic domains of previously described PTPs. An alignment of the amino acid sequence of the entire intracellular region of RPTPμ and other PTPs reveals an overall identity of 46% to LAR and 35–45% to other members.

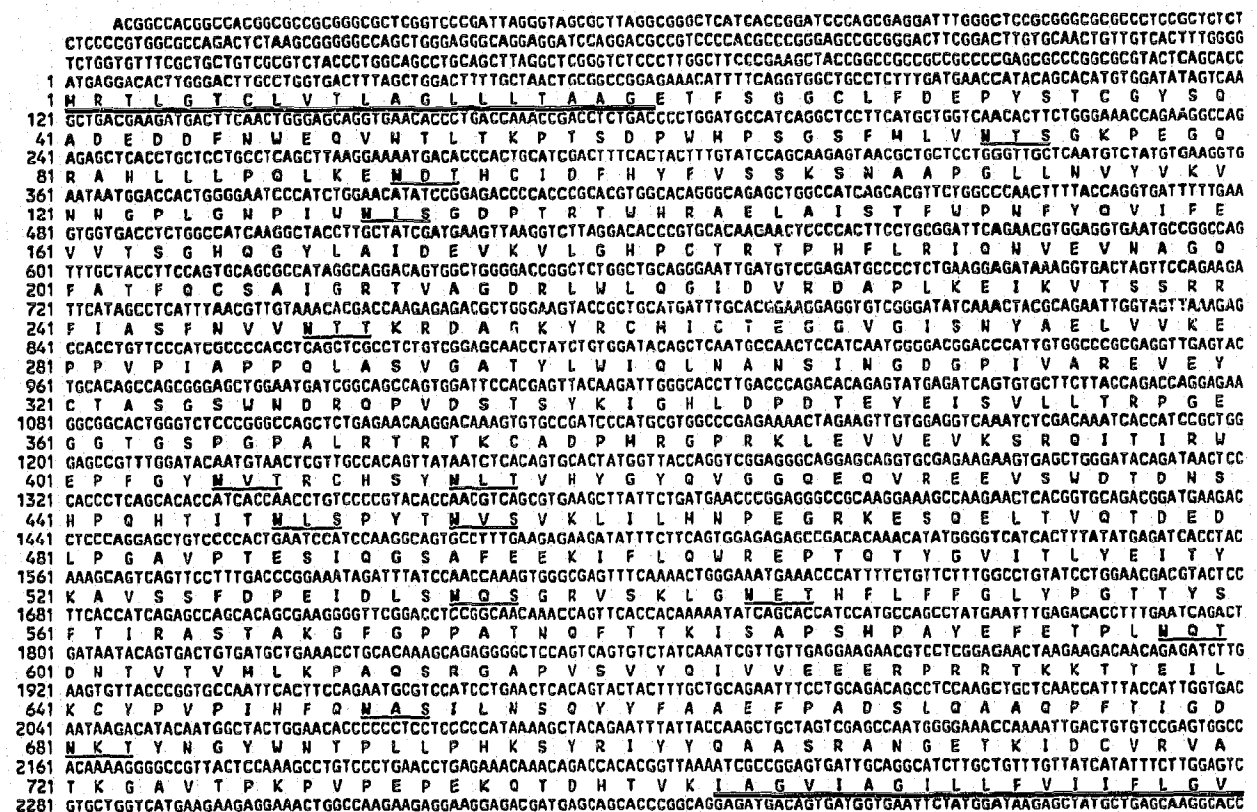

Fig. 2. cDNA nucleotide and its deduced amino acid sequence of mRPTPμ. The putative signal peptide and transmembrane region are heavily underlined. Potential *N*-linked glycosylation sites (N-X-S/T) are underlined. Both PTP domains are indicated with a shaded background.

The intracellular part of RPTPμ shows an unique feature among the known RPTPs in that the cytoplasmic stretch linking the transmembrane segment to the first catalytic domain is about 70 residues larger than in any other RPTP identified to date (158 versus 77–90 amino acids). This region is relatively rich in serine and threo-

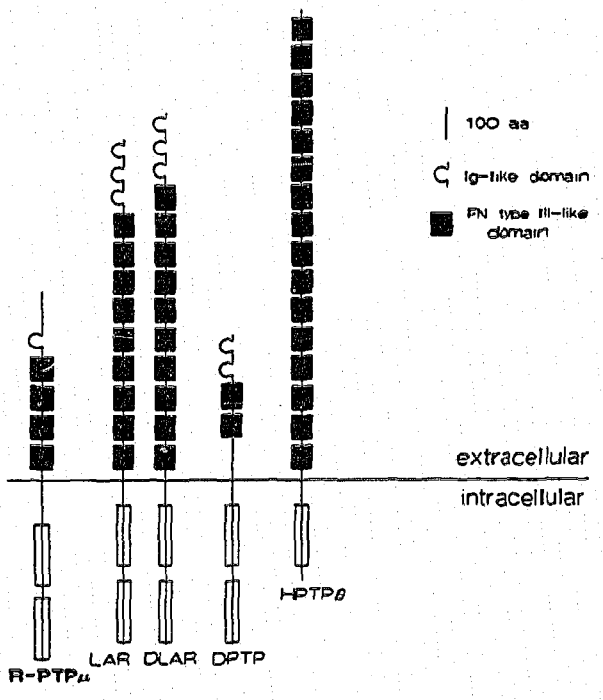

Fig. 3. Schematic comparison of several members of the RPTP family. Ig-like domains are represented by characteristic disulphide-linked structures. The small black boxes represent FN type III-like domains and the large open boxes represent the PTP domains. 'aa' denotes 'amino acids', DLAR, *Drosophila* LAR homologue, DPTP, *Drosophila* PTP (for reference see [17,18,24]).

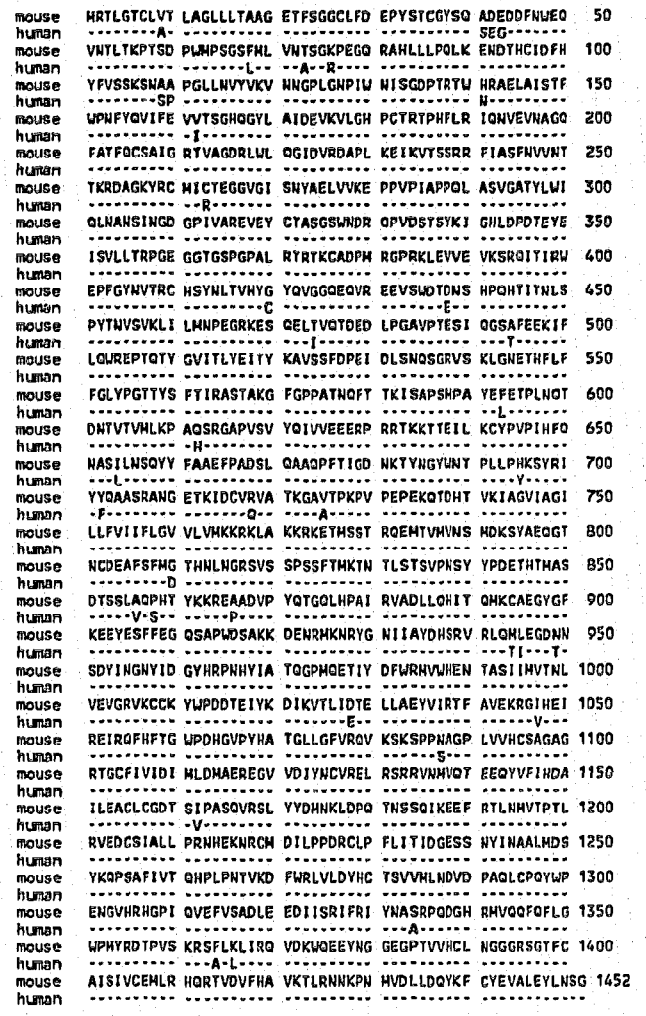

Fig. 4. Alignment of the mouse and human RPTPμ amino acid sequences. Identical amino acids are shown with a dashed line.

nine residues (20%), making regulatory phosphorylation a possibility.

The extracellular region of RPTPμ contains one Ig-like domain and 4 fibronectin (FN) type III-like domains. These structural motifs have previously been identified in LAR, HPTPβ, HPTPδ and in several other cell-surface molecules, such as the cell-adhesion molecule N-CAM [42] and the product of the tumor suppressor gene, DCC [43]. In addition to these motifs, the N-terminus of the predicted RPTPμ protein contains a stretch of 170 amino acids (residues 21–196) that shows no significant similarity to known sequences in the EMBL and GenBank databases. The deduced structure of the RPTPμ protein, as compared to that of several related RPTPs, is schematically shown in Fig. 3.

3.4. *Analysis of Human RPTPμ cDNA Clones*

The human RPTPμ cDNA sequence shows 88.5% bp identity to the mouse sequence. A comparison between both amino acid sequences is illustrated in Fig. 4. It is seen that mRPTPμ and hRPTPμ differ by only 37 amino acids, i.e. 98.7% sequence identity at the amino acid level.

3.5. *Distribution of the Mouse RPTPμ mRNA*

High stringency Northern analysis of total RNA of various mouse tissues, using an extracellular cDNA probe, reveals a single transcript of approximately 5.7 kb in lung and, at much lower levels, in brain and heart (Fig. 3). The size of the cloned cDNA is in good agreement with this transcript size.

3.6. *Transient Expression of the RPTPμ Protein*

While the cDNA sequence predicts a mature polypeptide of M_r 162 000, the apparent size of the expressed protein remains to be determined. We therefore transfected the mRPTPμ cDNA into COS-7 cells and after 48 h cell extracts were analyzed by immunoblotting, using antiserum Ab37 raised against a C-terminal peptide of 17 amino acids. As shown in Fig. 6 (lane 3), the antiserum recognizes a single protein of apparent M_r 195 kDa. Since the predicted size of the peptide backbone is about 162 kDa, the mature protein is likely to be glycosylated at many of the 13 putative *N*-glycosylation sites. We also transfected a truncated hRPTPμ

cDNA, lacking the external region, into COS cells (see section 2). In this case, a protein of the predicted molecular mass of 80 kDa was expressed (Fig. 6, lane 2).

3.7. *Chromosomal Localization of the Human RPTPμ Gene*

To determine the chromosomal localization of the human RPTPμ gene, an extracellular domain cDNA probe (bp 333–1985) was hybridized to a panel of 19 human–mouse or human–hamster cell lines containing various subsets of human chromosomes (Table I). From these hybridization results it is clear that the hRPTPμ gene must reside on chromosome 18. All cell lines containing chromosome 18 were scored positive for hRPTPμ, whereas all (except one) of the lines lacking this chromosome were negative. In one cell line a #18 rearrangement may have occurred after cell fusion resulting in lack of cytogenetic detection. For all other human chromosomes discordancy scores were invariably higher. In order to further refine RPTPμ gene localization, a hybrid cell line, obtained after fusion of t(X;18)(p11;q11) synovial sarcoma cells with a hamster cell line, containing the der(X) chromosome, was used. This line was negative for hRPTPμ which implies that hRPTPμ is located in the region 18pter-q11.

4. DISCUSSION

In this paper we describe the isolation and characterization of a cDNA encoding a novel receptor-like protein tyrosine phosphatase, RPTPμ. Since the first purification and sequencing of a cytosolic PTP by Tonks et al. [10,11], the number of cloned PTP cDNAs has increased steadily (for overview see [44,45]). The multigene nature of the PTP family suggests that these enzymes may act on distinct cellular substrates and that they are differentially regulated. In vitro studies have already indicated that different members of the family show different affinities for artificial substrates [18], but our understanding of the function and regulation of these enzymes is still in its infancy. Most of the newly identified PTPs have a receptor-like structure, strongly suggesting that these proteins act by transducing extracellular signals into the cell interior. The great diversity of their extracellular regions, varying between 27 and 1599 amino acids in length [44], suggests that there might be many different ligands regulating the activities of these enzymes. Although the nature of these extracellular signals is still unknown, studies with CD45, a leukocyte-specific RPTP, suggest a key role in signal transduction and growth control for RPTPs in general (for review see [46]). CD45, the best characterized RPTP at present, has a critical role in T-cell activation and proliferation. CD45 is thought to activate a *src*-like PTK, $p56^{lck}$, by dephosphorylation of a regulatory phosphotyrosine residue [47–50]. T cell clones lacking expression of CD45 are incapable of generating phosphoinositide-derived second messengers and fail to proliferate in response to T-cell receptor activation [27].

While the expression of CD45 is limited to cells of the hematopoetic lineage, other RPTPs, such as PTPα [19] and LAR [17], have a much wider tissue distribution, suggestive of a more general role. Expression of mRPTPμ is predominantly observed in lung, brain and heart, with little or no expression in other tissues, suggesting that its function may be restricted to certain cell types.The extracellular part of several RPTPμ, in common with that of LAR and a few other RPTPs, bears some structural similarities (Ig-like and FN type III-like domains) to cell-adhesion molecules, such as N-CAM. Although the functional significance of these common structural motifs is not yet clear, it has led to the widely discussed hypothesis that RPTPs may serve a function in cell–cell and/or cell–extracellular matrix interactions. On the other hand, it should be realized that Ig-like and FN type III-like domains are also found in receptors for soluble ligands [51], making conjectures about the nature of the ligand somewhat premature.

The great variety observed among the extracellular

Table I

Relationship between the presence of human chromosomes and human R-PTPμ in 19 human rodent somatic cell hybrid clones

Human Chromosome	Chromosome/R-PTPμ*				Discordancy**
	+/+	+/−	−/+	−/−	
1	8	3	3	5	32
2	6	0	5	8	26
3	7	2	4	6	32
4	9	3	2	5	26
5	9	3	2	5	26
6	5	4	6	4	53
7	6	3	5	5	42
8	8	5	3	3	42
9	5	3	6	5	47
10	4	4	7	4	58
11	7	4	4	4	42
12	6	4	5	4	47
13	5	2	6	6	42
14	7	3	4	5	37
15	7	4	4	4	42
16	10	4	1	4	26
17	17	7	4	1	58
18	10	0	1***	8	5
19	7	5	4	3	47
20	10	4	1	4	26
21	10	2	1	6	16
22	7	4	4	4	42
X	8	7	3	1	53

*Presence is indicated by +, absence is indicated by −.

**Calculated as $\frac{(+/-) + (-/+)}{19} \times 100\%$

***In one clone chromosome 18 was not observed via cytogenetic analysis. This may due to translocation or rearrangement after cell fusion.

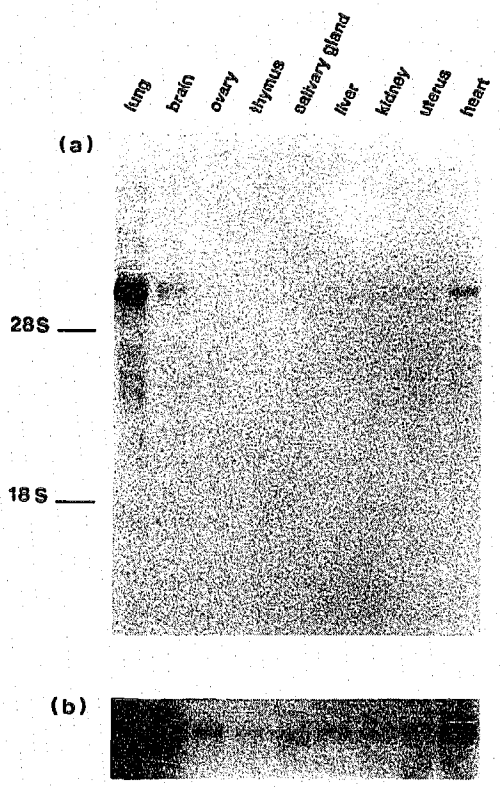

Fig. 5. Northern blot analysis of the mouse RPTPμ mRNA. Total RNA (15 μg per lane) prepared from the indicated mouse tissues was used for Northern blotting. The blot was hybridized with a cDNA probe coding for part of the extracellular domain of mRPTPμ. (A) 36 h exposure (using 2 intensifying screens). (B) 7 day exposure (using 2 intensifying screens).

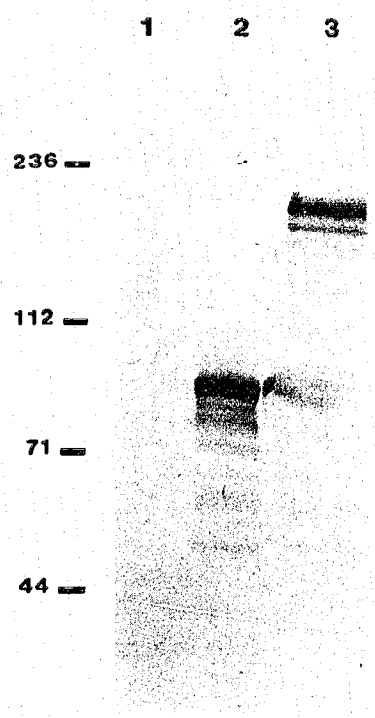

Fig. 6: Immunoblot analysis of the RPTPμ protein. Transiently transfected COS cells were analyzed for RPTPμ expression as described in section 2. Lane 1, lysates of cells tranfected with vector pMT2m without insert. Lane 2, lysates of cells transfected with pMT2TR containing a truncated form of the hRPTPμ cDNA. Lane 3, lysates of cells transfected with pMT2mFL containing a full length mRPTPμ cDNA. Sizes of molecular mass markers are shown in kDa.

regions of the RPTPs is in marked contrast to the conservation of the intracellular catalytic domains. It remains to be investigated whether the various catalytic domains of RPTPs have distinct substrate specificities involving specific PTKs, their tyrosine phosphorylated substrates, or both. Knowledge of the RPTPμ primary sequence should now permit delineation of its biochemical and biological activities and elucidation of its presumed role in signal transduction.

The possibility that PTPs may function as tumor-suppressor genes is consistent with current knowledge about mechanisms of cellular growth control. Direct evidence for this notion comes from a recent study showing that the gene for PTPγ, a partially cloned RPTP, has characteristics of a candidate tumor suppressor gene at human chromosome 3p21 [52]. Our results indicate that the human RPTPμ gene maps to chromosome 18, region pter-q11. This region is of particular interest since cytogenetic aberrations within this region are frequently encountered in various neoplastic disorders, particularly colon carcinoma [53], synovial carcinoma [54] and malignant lymphoma [55]. In situ hybridization studies using a genomic clone are in progress to further refine the determination of the chromosomal locus of the RPTPμ gene. Knowledge of the precise chromosome locus, along with comparative studies in normal and malignant cells, may help to establish whether RPTPμ can function as a growth suppressor and may play a role in tumorigenesis.

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