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Cloning, expression and chromosomal localization of a novel human dipeptidyl peptidase (DPP) IV homolog, DPP8

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Dipeptidyl peptidase (DPP) IV has roles in T-cell costimulation, chemokine biology, type-II diabetes and tumor biology. Fibroblast activation protein (FAP) has been implicated in tumor growth and cirrhosis. Here we describe DPP8, a novel human postproline dipeptidyl aminopeptidase that is homologous to DPPIV and FAP. Northern-blot hybridization showed that the tissue expression of *DPP8* mRNA is ubiquitous, similar to that of DPPIV. The *DPP8* gene was localized to chromosome 15q22, distinct from a closely related gene at 19p13.3 which we named *DPP9*. The full-length *DPP8* cDNA codes for an 882-amino-acid protein that has about 27% identity and 51% similarity to DPPIV and FAP, but no transmembrane domain and no N-linked or O-linked glycosylation. Western blots and confocal microscopy of transfected COS-7 cells showed DPP8 to be a 100-kDa monomeric protein expressed in the cytoplasm. Purified recombinant DPP8 hydrolyzed the DPPIV substrates Ala-Pro, Arg-Pro and Gly-Pro. Thus recombinant DPP8 shares a postproline dipeptidyl aminopeptidase activity with DPPIV and FAP. DPP8 enzyme activity had a neutral pH optimum consistent with it being nonlysosomal. The similarities between DPP8 and DPPIV in tissue expression pattern and substrates suggests a potential role for DPP8 in T-cell activation and immune function.

Keywords: dipeptidyl peptidase; fibroblast activation protein; postproline peptidase; prolyl oligopeptidase; serine proteinase.

Very few enzymes are able to cleave the prolyl bond. The most widely studied of these enzymes is a 766-amino-acid, type-II integral membrane protein dipeptidyl peptidase (DPP) IV (EC 3.4.14.5). DPPIV also has a soluble form that lacks the transmembrane domain [1,2]. The tertiary structure of DPPIV contains an N-terminal seven-blade β-propeller domain and a C-terminal α/β-hydrolase domain [3]. DPPIV cleavage of specific substrates results in alterations in their biological activities. These substrates include certain chemokines, growth factors such as glucagon and glucagon-like peptides 1 and 2, neuropeptides including neuropeptide Y and substance P and vasoactive peptides [4–6]. The N terminal truncation of the chemokines RANTES (regulated on activation normal T cell expressed and secreted), eotaxin, macrophage-derived chemokine and stromal-cell-derived factor-1 alters the receptor specificities of these chemokines, potentially altering the Th1/Th2 balance of an immune response towards Th1 [5].

DPPIV/CD26 expression is ubiquitous but is significantly upregulated on activated T, B and NK cells [7–11]. The role of DPPIV/CD26 in immune activation involves both its enzyme activity and its non-catalytic activity, which is the ability to bind adenosine deaminase [5,12–14]. DPPIV is in the peptidase family S9b, which along with prolyl endopeptidase (PEP, S9a) and acylaminoacyl peptidase (S9c) [15] form the prolyl oligopeptidase family. We have proposed that DPPIV, fibroblast activation protein (FAP) [16,17] and dipeptidyl aminopeptidase-like protein (DPP6) [18] form a *DPPIV*-like gene family which corresponds to peptidase family S9b [19]. We have compared DPPIV and FAP in detail [5]. FAP is selectively expressed by stromal fibroblasts of tumors and healing wounds [16] and by activated hepatic stellate cells [20]. FAP has postproline dipeptidyl aminopeptidase activity similar to but distinct from that of DPPIV, has gelatinase activity and binds to $\alpha_3\beta_1$ and $\alpha_5\beta_1$ integrin [20–24].

Recently, novel enzymes have been reported with substrate specificities similar to DPPIV. DPPIV-β is a cell surface glycoprotein of 82 kDa that binds DPPIV inhibitors but with less affinity than DPPIV, and no sequence data for this enzyme is available [25]. Attractin (DPPT-L) is a 175-kDa soluble glycoprotein reported to hydrolyze Gly-Pro [26]. Attractin

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Abbreviations: DPP, dipeptidyl peptidase; EST, expressed sequence tag; FAP, fibroblast activation protein; G3PDH, glyceraldehyde-3-phosphate dehydrogenase; NA, nitroanilide; PEP, prolyl endopeptidase; PBMC, peripheral blood monocyte; stPBMC, peripheral blood monocyte stimulated with phytohaemagglutinin.

Enzymes: dipeptidyl peptidase IV (P27487, EC 3.4.14.5); prolyl endopeptidase (P48147, EC 3.4.21.26); acylaminoacyl peptidase (P13798, EC 3.4.19.1); fibroblast activation protein (GenPept: g1888316); DPPIV-β; attractin (GenPept: g3676347); quiescent peptidyl peptidase (GenPept: g6465985); *N*-acetylated alpha-linked acidic dipeptidase II (GenPept: g4539525).

Note: nucleotide sequences reported in this paper have been submitted to the GenBank™ databank with accession numbers AF221634, AF221635, AF221636, AF221637.

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contains a kelch repeat domain [27] and shares no significant sequence homology with DPPIV or any other peptidase. Two other peptidases have been reported to hydrolyze Gly-Pro, but are structurally unrelated to DPPIV: the carboxypeptidase, quiescent peptidyl peptidase [28], and the glutamate carboxypeptidase, N-acetylated alpha-linked acidic dipeptidase II [29]. Thus, new enzymes of this family or enzymes of similar function but different structure are emerging. Judging from the critical roles of DPPIV and FAP in biological processes of cellular activation, inflammation and tissue remodeling, additional family members are likely to play a similar role in these and other biological processes. Hence the aim of this study was to characterize a novel peptidase related to DPPIV in both substrate specificity and structure.

This study describes the cloning of a full-length cDNA, chromosomal localization, expression and functional characterization of a novel human peptidase, dipeptidyl peptidase 8 (DPP8). Biochemical characterization of this novel protein revealed that it has enzyme activity similar to that of DPPIV and FAP and is upregulated during immune activation.

EXPERIMENTAL PROCEDURES

General

Restriction and other enzymes used in cloning were obtained from Boehringer Mannheim Roche. Standard molecular biology techniques were used [30] unless indicated otherwise. The collection of specimens used in this study was approved by the Royal Prince Alfred Hospital human ethics committee.

Cell culture and RNA preparation

Human peripheral blood monocytes (PBMCs) were isolated by Ficoll-Hypaque density-gradient centrifugation (Amersham Pharmacia Biotech, Uppsala, Sweden) of blood obtained from healthy donors. The PBMCs were incubated in AIM-V medium (Life Technologies, Gaithersburg, MD, USA) supplemented with 2 mM L-glutamine and were stimulated with either 1 $\mu g \cdot mL^{-1}$ phytohaemagglutinin (Wellcome) or 100 $ng \cdot mL^{-1}$ OKT3 (Orthoclone, Ortho Biotec Ravitan, NJ, USA) for 72 h. The human cell lines Jurkat, CCRF-CEM, Raji, Daudi and HepG2 were grown to confluence in Dulbecco's modified Eagle's medium (Trace Biosciences, Sydney, NSW, Australia) supplemented with 10% fetal bovine serum and 2 mM L-glutamine.

Liver and placental RNA were prepared from snap-frozen human tissue as described previously [31]. However, RNA was prepared from PBMCs and cell lines using an RNAeasy kit (Qiagen, Hilden, Germany).

Bioinformatics

BLAST searches [32] and all multiple sequence alignments were performed through the Australian National Genomic Information Service (ANGIS, Sydney, NSW, Australia). PILEUP (GCG Version 8, Genetics Computer Group, Madison, WI, USA) was used for multiple sequence alignments of proteins.

A BLAST search was performed on the public expressed sequence tag (EST) database using the complete human *DPPIV* (GenBank™ accession number X60708) and *FAP* (accession number U09278) nucleotide sequences as query sequences. An EST clone (accession number AA417787) was obtained from the American Type Culture Collection. The DNA insert of this clone was sequenced on both strands using automated sequencing at SUPAMAC (Sydney, NSW, Australia). Because of its homology with DPPIV, this new gene was named dipeptidyl peptidase 8 (DPP8).

Cloning of *DPP8* cDNA

The DPP8 EST sequence was used to design the forward primer, DPP8-pr1 (CAAATAGAAATTGACGATCAGGTG) and the reverse primer DPP8-pr2r (TCTTGAAGGTAGTG-CAAAAGATGC) for PCR from the EST cDNA. The PCR conditions were 94 °C for 5 min, followed by 35 cycles of 94 °C for 1 min, 55 °C for 30 s and 70 °C for 1 min. This 484-bp PCR product was gel-purified, ^{32}P-labeled using a Megaprime Labeling Kit (Amersham Pharmacia Biotec) and hybridized to a Master RNA blot (Clontech, Palo Alto, CA, USA), which contained poly(A)-rich RNA from 50 adult and fetal tissues immobilized in dots, in accordance with the manufacturer's instructions. The 484-bp DPP8 PCR product was used to screen a human placental λ STRETCH PLUS library (Clontech) using standard methods. For the tertiary screen, the clones contained in λTriplEx were converted into pTriplEx plasmids and transformed into BM25.8 *Escherichia coli* recipient bacteria. The clones were retransformed into MC1061 *E. coli* for subsequent DNA purification. The DNA was then sequenced using M13 forward and reverse and primer walking.

5′ RACE

A 5′ RACE version 2.0 kit (Life Technologies) was applied to phytohaemagglutinin-stimulated PBMC (stPBMC) and placental RNA according to the kit instructions. The sequence of the T8 library clone was used to design GSP1 (TCCTTCCTTCAG-CATCAATC) and GSP2 (CTTAAAAGTGACTTTAG-GATTTGCTGTACC). 5′ RACE PCR products were cloned into pGEM-T Easy® vector (Promega, Madison, WI, USA) and sequenced using M13 forward and reverse primers and by primer walking. To confirm that the 5′ RACE product was *DPP8*, RT-PCR on stPBMC RNA used the primers DPP8-pr23 (GGAAGAAGATGCCAGATCAGCTGG) and DPP8-pr19r (TCCGTGTATCCTGTATCATAGAAG) to span the junction between the 5′ RACE product and the EST clone AA417787. This PCR yielded two products, stPBMCdy3-2-1 (1602 bp) and stPBMCdy3-3-10 (1083 bp), which were gel purified and cloned into pGEM-T Easy® and subsequently sequenced.

Subcloning of *DPP8* cDNA into a pcDNA3.1/V5/His expression vector

The stPBMC RACE product, the stPBMCdy3-2-1 (1602 bp) junction fragment and the library clone T21 were joined together and cloned into the expression vector pcDNA3.1/V5/HisA (Invitrogen BV, Groningen, the Netherlands). This created a *DPP8* cDNA of 3.1 kb with an ORF of 882 amino acids. The first construct was made using three sequential cloning steps. First, an *Eco*RV–*Xba*I fragment of T21 (containing 3′ DPP8, stop codon and 3′ UTR on *DPP8* cDNA) was ligated into *Eco*RV–*Xba*I-digested pcDNA3.1/V5/HisA vector. Secondly, an *Eco*RI–*Eco*RV fragment of stPBMCdy3-2-1 was then added to this construct digested with *Eco*RI–*Eco*RV. Finally the 5′ RACE product was cut with *Eco*RI and cloned into the *Eco*RI site of the previous construct to form the complete 3.1-kb *DPP8* cDNA. This construct, pcDNA3.1–DPP8, expressed DPP8 protein with no tag.

In addition, the stop codon in the DPP8 expression construct in pcDNA3.1/V5/HisA was altered using PCR to

create a C-terminal fusion with the V5 and His tag contained in the vector. This construct was named pcDNA3.1-DPP8/V5/His. All expression constructs subcloned into pcDNA3.1/V5/His were verified by full sequence analysis.

Chromosomal localization of *DPP8* by fluorescence *in situ* hybridization analysis

DPP8 was localized using two different probes, the *DPP8* EST and the T8 clone. The probes were nick-translated with biotin-14-dATP and hybridized *in situ* at a final concentration of 10 ng·μL^{-1} to metaphases from two normal males. The fluorescence *in situ* hybridization method was modified from that previously described [33] in that chromosomes were stained with both propidium iodide and 4,6-diamidino-2-phenylindole.

DPP8 gene expression analyzed by Northern blot

Human multiple-tissue Northern blots (Clontech) containing 2 μg poly(A)-rich RNA were prehybridized in Express Hybridization solution (Clontech) for 30 min at 68 °C. Both the DPP8 484-bp product and the 5′ RACE stPBMC product were radiolabeled using the Megaprime Labeling kit and [^{32}P]dCTP (NEN Life Science, Boston, MA, USA). Unincorporated label was removed using a NICK column (Amersham Pharmacia Biotech), and the denatured probe was incubated with the blot for 2 h at 68 °C in Express Hybridization solution. Washes were performed at high stringency, and blots exposed to BIOMAX MS film overnight with a BioMax (Kodak, Rochester, USA) MS screen at −70 °C.

Expression of *DPP8* in human lymphocytes and cell lines

RNA (1 μg) was reverse-transcribed using the Superscript II enzyme kit (Gibco–BRL) as described previously [34]. PCR using DPP8-pr18 (CTGTGACGCCACTAATTATCTATG) as the forward primer and DPP8-pr26R (CCTAGAGAGGCTAGGGTATTCAAG) as the reverse primer was used to detect full-length *DPP8* mRNA. The glyceraldehyde-3-phosphate dehydrogenase (G3PDH) control primer set was G3PDH for (ACCACAGTCCATGCCATCAC) and G3PDHrev (TCCACCACCCTGTTGCTGTA) to give a 470-bp product.

cDNA (diluted 1 : 4; 1 μg) was amplified in a 25-μL PCR mixture which contained: 0.2 mM dNTPs, 0.125 unit Amplitaq Gold enzyme (PerkinElmer), 1 × buffer II (Perkin–Elmer), 1.5 mM $MgCl_2$ and 100 ng·mL^{-1} each primer. The 35-cycle PCR was performed as follows: denaturation at 94 °C for 1 min, primer annealing at 55 °C for 30 s, and an extension step at 72 °C for 1 min. The amplified products were analyzed by electrophoresis of 15 μL PCR mixture on a 3 : 1 Nusieve gel (FMC Bioproducts, Rockville, MD, USA) plus 0.5 μg·mL^{-1} ethidium bromide in Tris/acetate/EDTA buffer (0.04 M Tris/acetate, 0.001 M EDTA, pH 8.0).

Transfection, Western blot, immunocytochemistry, cytochemistry and flow cytometry

Monkey kidney fibroblast (COS-7) cells (American Type Culture Collection, CRL-1651) were grown and transfected as described previously [3]. For making stable cell lines, Geneticin (G418; Life Technologies) was added to the medium, beginning 24 h after transfection. COS cell extracts were prepared by sonication followed by differential centrifugation and neither boiled nor reduced before SDS/PAGE (10% gel) and transfer to nitrocellulose, as described previously [1,20]. The presence of DPP8 fused with the V5 epitope was detected using an anti-V5 mAb (Invitrogen). COS cell monolayers were fixed in cold ethanol before staining with anti-V5 mAb [3,9,20]. Some monolayers were fixed in 4% paraformaldehyde and permeabilized with 0.1% Triton X-100 [35], then double-stained with wheat germ agglutinin to label Golgi apparatus and with goat anti-mouse IgG to label DPP8, conjugated to Alexa Fluor 488 and Alexa Fluor 594, respectively (Molecular Probes, Eugene, OR, USA). Flow cytometry and confocal scanning microscopy using a Leica TCS-NT confocal microscope have been described previously [3,20].

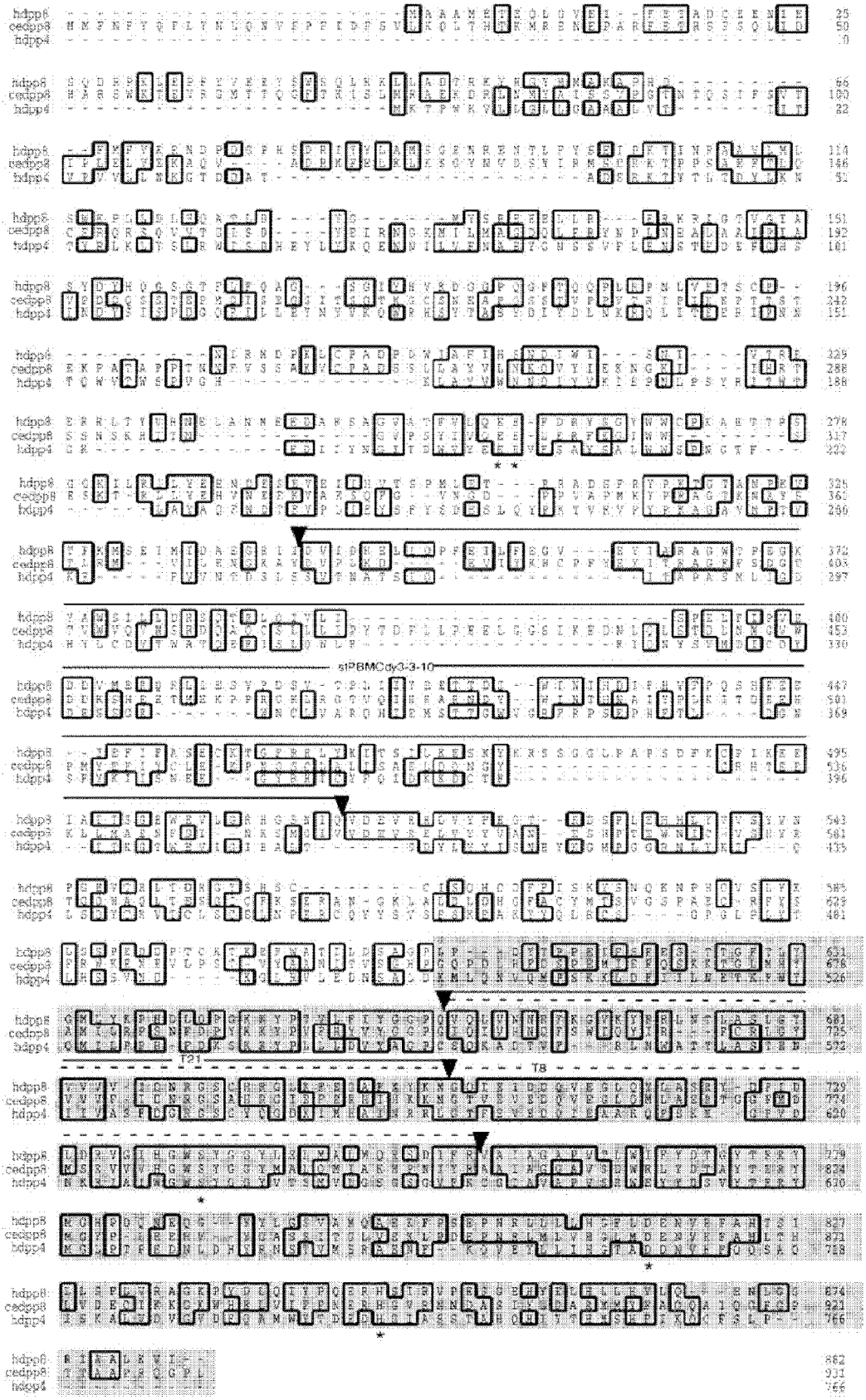
Purification of recombinant DPP8/V5/His and DPPIV/V5/His

Cells (1×10^7) expressing each protein were sonicated in native buffer (50 mM sodium phosphate, 300 mM NaCl), then treated with 700 U DNAse for 20 min at room temperature. DPPIV is expressed at the cell surface, so 1% Triton X-100 was used to solubilize DPPIV/V5/His. Insoluble material was removed by centrifugation. The supernatant was incubated with 1 mL Talon® Metal Affinity Resin (Clontech) following the manufacturer's instructions for a batch/gravity flow procedure. The resin was washed with 50 mM sodium phosphate, containing 300 mM NaCl and 5 mM imidazole, and proteins were eluted using the same buffer containing 150 mM imidazole. Enzyme activity was used to monitor eluted fractions.

Enzyme assays

Enzyme assays were performed as described previously [19]. Either clarified cell extract from 1×10^4 sonicated COS-7 cells or purified protein derived from 1×10^5 cells was incubated with substrate in 70 μL phosphate buffer, pH 7.4, for 30 min at 37 °C, except where otherwise indicated. The specific DPPIV substrates Gly-Pro-toluenesulfonate, H-Gly-Pro-*p*-nitroanilide (NA)/HCl (Sigma, St Louis, MO, USA) and Gly-Pro-7-amino-4-trifluromethylcoumarin (Calbiochem, San Diego, CA, USA) were tested. Other substrates tested were H-Ala-Pro-pNA/HCl, H-Arg-Pro-pNA acetate salt, H-Lys-Ala-pNA.2HCl, H-Asp-Pro-pNA, H-Ala-Ala-pNA/HCl, H-Ala-Ala-Pro-pNA/HCl, H-Ala-Ala-Phe-pNA, succinyl-Ala-Pro-pNA, H-Ala-Phe-Pro-pNA and Z-Ala-Pro-p-NA from Bachem AG (Bubendorf, Switzerland). H-Ala-Pro-4-methoxyβNA/HCl, Z-Lys-Pro-4-methoxyβNA formate salt, H-Lys-Pro-4-methoxy

Fig. 1. Alignment of the deduced amino-acid sequence of DPP8 with the *C. elegans* homolog of DPP8 and human DPPIV. Amino-acid residues are numbered in the right margin. Amino-acid residues identical in all three proteins are boxed. Asterisks mark the putative catalytic triad residues and the two glutamates of the β-propeller domain essential for DPPIV enzyme activity [19]. The gray shading denotes the α/β-hydrolase domain of these proteins. Filled triangles joined by lines indicate starts and ends of alternatively spliced transcripts, stPBMCdy3-3-10 (solid lines), T8 (dashed lines) and T21 (solid lines). This alignment was constructed using the PILEUP program in GCG.



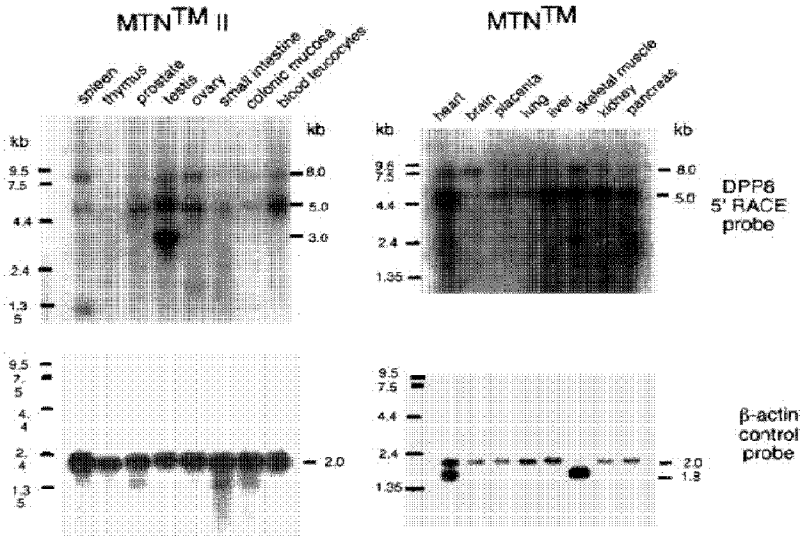


Fig. 2. Northern-blot analysis of *DPP8* expression. Human multiple-tissue Northern (MTN) blots (Clontech) containing 2 μg per lane of poly(A)-rich RNA were hybridized with a ^{32}P-labeled *DPP8* probe at 68 °C and washed at high stringency. Autoradiographic exposure was overnight at −70 °C with a BioMax MS screen. Size markers are indicated in kb on the left of each autoradiogram.

βNA/HCl, Z-Ala-Pro-4-methoxyβNA, H-Gly-Pro-βNA and H-His-Ser-4-methoxyβNA acetate salt (Bachem AG) were tested for their ability to stain unfixed transfected cells.

All inhibitors were incubated with each purified enzyme in phosphate buffer, pH 7.4, for 15 min before the addition of substrate. After the addition of 1 mM H-Ala-Pro-pNA substrate for purified DPP8 and 1 mM H-Gly-Pro-pNA substrate for purified DPPIV, samples were incubated for 60 min at 37 °C. All enzyme assays were performed in triplicate.

RESULTS

Molecular cloning and sequence analysis of *DPP8* cDNA

The EST AA417787, derived from human tonsil, contained an insert 795 bp in length, encompassing 527 bp of coding sequence, a TAA stop codon and 258 bp of 3′ noncoding sequence. The 178 amino acids encoded by this sequence had 36% amino-acid identity with and 58% amino-acid similarity to a C-terminal portion of human DPPIV. A BLASTp search into protein databases revealed that the EST AA417787 had 46% amino-acid identity with and 70% amino-acid similarity to an uncharacterized *Caenorhabditis elegans* protein which we called the *C. elegans* homolog of DPP8 (accession number g2804453).

The Master RNA blot revealed that *DPP8* had ubiquitous mRNA expression, with the most intense hybridization signals in testis and placenta (data not shown). Only two of 23 clones obtained by screening a placental cDNA library contained 5′ sequence additional to that of the *DPP8* EST. These cDNA clones were designated T8 (accession number AF221636) and T21(accession number AF221635), and were 1669 bp and 1197 bp, respectively. In addition, comparison of these sequences with the *DPP8* EST revealed that the T8 cDNA lacked a 153-bp (51-amino-acid) region that was present in both the T21 cDNA and the *DPP8* EST. Significantly, this 51-amino-acid region includes the catalytic serine (Fig. 1).

The 5′ RACE technique was applied to both stPBMC RNA and placental RNA to obtain the 5′ end of the *DPP8* gene. The 5′ RACE product obtained from stPBMC RNA was 0.2 kb larger than that from placental RNA but otherwise identical. The first methionine within a Kozak sequence was found 214 bp from the 5′ end of the stPBMC RACE product. To confirm the identity of the 5′ RACE product as the 5′ of *DPP8*, RT-PCR was carried out on a region spanning the junction between the 5′ RACE product and the T8 cDNA library clone. The RT-PCR on stPBMC RNA produced two clones, stPBMCdy3-2-1 and stPBMCdy3-3-10. Compared with T8 and T21, both clones had an additional insert region of 144 bp (48 amino acids) immediately adjacent to the splice site of T8. Sequence homology analysis of this additional insert region found an homologous region in both DPPIV and the *C. elegans* homolog of DPP8. This indicated that the library clones T8 and T21 represented splice variants of *DPP8*. Furthermore, the smaller clone stPBMCdy3-3-10 (accession number AF221637) was found to represent a third splice variant of *DPP8* as it contained a 519-bp deletion at the 5′ end which would result in a deletion of 175 amino acids.

A full-length *DPP8* clone (accession number AF221634) was constructed using the larger 5′ RACE product, stPBMCdy3-2-1, and clone T21. This generated a putative *DPP8* cDNA of 3.1 kb (including 5′ and 3′ UTRs) with an ORF of 882 amino acids. This 882-residue putative *DPP8* protein contained no N-linked or O-linked glycosylation sites, and Kyte–Doolittle hydrophobicity analysis showed no potential transmembrane domain, unlike DPPIV, FAP and DPP6.

Human DPP8 protein is homologous with both human DPPIV (51% amino-acid similarity, 27% amino-acid identity) and human PEP (46% amino-acid similarity, 21% amino-acid identity). Significant homology (55% similarity, 32% identity) was observed between human DPP8 and the *C. elegans* homolog of DPP8 (Fig. 1). A BLASTn search into GenBank revealed that the *DPP8* gene had high homology with two overlapping cosmids, accession numbers AC005594 and AC005783. These cosmids encode a region of the human chromosome at 19p13.3. The gene located in this region is 39.5 kb in size, contains 19 exons, and encodes a protein of ≈ 913 amino acids. The hypothetical protein encoded by the two cosmids shared the greatest homology (76% similarity, 58% identity) observed with *DPP8* and so was named DPP9. The gene structure of *DPP9* was elucidated (data not shown).

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