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Review

PTN (pleiotrophin)

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Identity

Other names: HARP, HBGF8, HBNF, NEGF1

HGNC (Hugo): PTN

Location: 7q33

Note

The different names initially assigned to the growth factor were due to its purification from different tissues in different labs. The name pleiotrophin is widely accepted nowadays and reflects the plethora of functions it exerts in different tissues and cell lines (see "Function").

The mouse gene is located on chromosome 6 (Tezuka et al., 1990), the rat (Merenmies and Rauvala, 1990), bovine (Li et al., 1990; Böhlen et al., 1991), and zebrafish (Chang et al., 2004) on chromosome 4, the fruit-fly (Englund et al., 2006) and monkey genes on chromosome 3, the chicken gene on chromosome 1 (Lee et al., 2012), the canine gene on chromosome 16.

Note that the records' status and the GenBank sequence data for these species are defined as provisional or model.

DNA/RNA

Description

The human gene coding PTN was first found to consist of at least 7 exons, with the open reading frame (ORF) located on 4 exons (Lai et al., 1992). In another study it was reported to be arranged in 5 exons and 4 introns (Milner et al., 1992).

PTN mRNA is approximately 1,6 kb. The ORF of the coding region is 507 bp.

Transcription

Although a variant with a single residue deletion has been mentioned (Kretschmer et al., 1993), it is considered that no mRNA variants exist (Laaroubi et al., 1995). There are two PTN transcripts appearing in Ensembl.

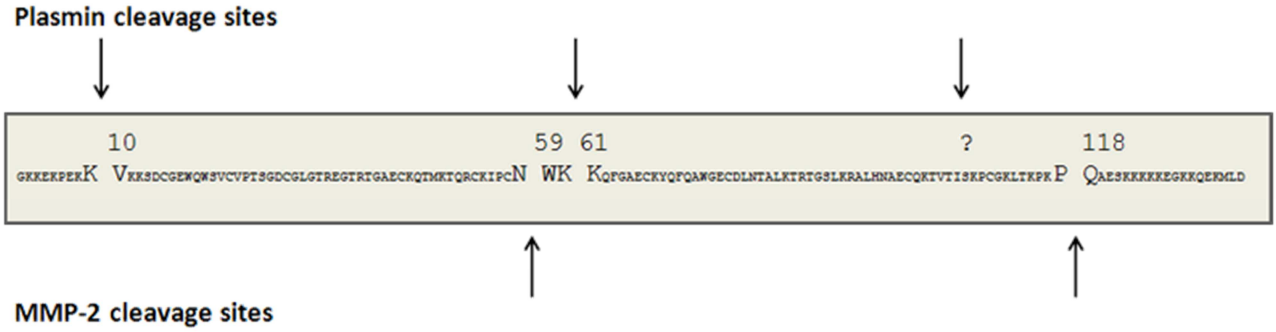
Pseudogene

None known.

Protein

Note

PTN does not possess an N-glycosylation consensus sequence, nor have any other co- or post-translational modifications been observed up to date. However, a controversy for the cleavage site of the signalling peptide has been documented in the literature, identifying a 136- or a 139-amino acid residue mature protein (Laaroubi et al., 1994; Delbé et al., 1995). Proteolytic cleavage of PTN has been described by plasmin (Polykratis et al., 2004) and MMP-2 (Dean et al., 2007), leading to peptides with different biological activities concerning tumour growth and angiogenesis. Two forms of PTN that differ by 12 amino acid residues in the C-terminal (15 and 18 kDa, designated as PTN15 and PTN18, respectively) have been detected in glioblastoma (Lu et al., 2005) and are considered to result from post-translational processing, e.g. proteolysis.



Proteolytic cleavage of PTN. The arrows indicate the cleavage sites by plasmin (Polykratis et al., 2004) and MMP-2 (Dean et al., 2007) and the residues where the cleavages occur are highlighted. The numbers indicate the corresponding residues.

Description

Structure. PTN is a secreted growth factor composed of 168 amino acid residues; the first 32 correspond to the secretory signal sequence and the remaining 136 residues constitute the mature protein. Although the calculated molecular weight of PTN is 15,3 kDa, it appears as an 18 kDa band on gels, suggesting an anomalous migration due to the high percentage of basic amino acid residues.

Heteronuclear NMR has revealed the structure of PTN (Kilpelainen et al., 2000); two β-sheet domains (N- and C-terminals) maintained through five disulfide bonds and connected by a flexible linker, and two lysine-rich clusters at the N- and C-terminal domains that appear as random flexible coils. Each β-sheet domain consists of three antiparallel β-strands and contains a thrombospondin repeat I (TSR-I) motif. TSR-I has been suggested to be responsible for PTN binding to heparin/heparan sulfate (Raulo et al., 2005) and N-syndecan (Raulo et al., 2006), to regulate PTN neurite outgrowth activity and synaptic plasticity (Raulo et al., 2006), mitogenic and angiogenic activity (in particular the C-terminal TSR-I) (Hamma-Kourbali et al., 2008). Computational analysis has identified the three-dimensional structure and electrostatic potential distribution of PTN, and homology modelling using midkine as a template has predicted the binding pocket of PTN for oligosaccharides (Li et al., 2010a). The structure of PTN peptide P112-136 has also been studied by NMR suggesting that the peptide adopts a specific folded conformation (Mikelis et al., 2011).

Cloning of different PTN constructs has led to the identification that residues 41-64 (with the cooperation of either of the lysine-rich terminal clusters) are important for the transformation of NIH 3T3 cells and were designated as the "transforming domain" (Zhang et al., 1999b), while residues 69-136 have been designated as the "angiogenesis domain" (Zhang et al., 2006) (also see "Peptides/chimaeras and structure-function relationship").PTN has been reported to form non-covalent dimers in a process dependent on the presence of heparin or other glycosaminoglycans (Bernard-Pierrot et al., 1999). PTN was secreted as a dimer in conditioned medium of NIH 3T3 cells (Bernard-Pierrot et al., 1999). Furthermore, truncated PTN mutants (P1-40 and P1-110) have been suggested to heterodimerize with endogenous PTN (Zhang et al., 1997; Bernard-Pierrot et al., 2002), an action that explains their dominant negative effects.

Regulation. PTN expression is regulated in a temporal and cell type-dependent manner (also see "Expression"). PTN expression has been reported to be regulated by: cytokines and growth factors, such as midkine in a compensatory manner (Herradon et al., 2005), platelet-derived growth factor (PDGF) (Li et al., 1992a; Antoine et al., 2005), epidermal growth factor (Pufe et al., 2003), fibroblast growth factor (FGF) 2 (Hatziapostolou et al., 2006), and tumour necrosis factor α (Pufe et al., 2003); signalling molecules, such as cAMP (Mourlevat et al., 2005), hydrogen peroxide (Polytarchou et al., 2005) and nitric oxide (Polytarchou et al., 2009); hormones (Tamura et al., 1995; Vacherot et al., 1995; Roger et al., 2006); transcription factors, such as AP-1 (Florin et al., 2005; Polytarchou et al., 2005; Poimenidi et al., 2009) and HOXA5 (Chen et al., 2005); tumour suppressors, such as menin (Gao et al., 2009; Feng et al., 2010) and PTEN (Li et al., 2006); miscellaneous conditions, such as hypoxia (Antoine et al., 2005), mechanical loading (Liedert et al., 2004), serum (Poimenidi et al., 2009) and X-rays (Polytarchou et al., 2004). Contradictory observations regarding retinoic acid suggest either induction of expression by retinoic acid (Kretschmer et al., 1991; Bloch et al., 1992; Azizan et al., 2000; Brunet-de Carvalho et al., 2003; Mitsiadis et al., 2008) and regulation by the retinoic acid receptors (Marzan et al., 2011), or lack of effect (Li et al., 1992a). PTN expression is also altered during disease (see "Implicated in").

PTN has been suggested to mediate FGF2 stimulatory effect on human prostate cancer cell proliferation and migration (Hatziapostolou et al., 2006), as well as hydrogen peroxide and nitric oxide stimulatory effects on human prostate cancer and endothelial cell migration (Polytarchou et al., 2005; Polytarchou et al., 2009). It is also suggested to regulate vascular endothelial growth factor (VEGF) receptor expression (Kokolakis et al., 2006) and VEGF-mediated proliferation and angiogenesis of endothelial cells (Héroult et al., 2004).

Signalling. PTN acts via various receptors (reviewed in Papadimitriou et al., 2009), like the receptor protein tyrosine phosphatase beta/zeta (RPTPβ/ζ) (Maeda et al., 1996; Meng et al., 2000; Ulbricht et al., 2003; Lu et al., 2005; Perez-Pinera et al., 2007b; Herradón and Ezquerra, 2009; Koutsioumpa et al., 2009; Mikelis et al., 2009; Polytarchou et al., 2009), $\alpha_v\beta_3$ integrin (Mikelis et al., 2009; Feng et al., 2010; Mikelis et al., 2011), nucleolin (Take et al., 1994; Said et al., 2005; Koutsioumpa et al., 2012), N-syndecan (Raulo et al., 1994; Nolo et al., 1995; Kinnunen et al., 1998a; Raulo et al., 2006; Landgraf et al., 2008) and anaplastic lymphoma kinase (ALK) (Stoica et al., 2001; Bowden et al., 2002; Powers et al., 2002; Lu et al., 2005; Perez-Pinera et al., 2007c; Yanagisawa et al., 2010).

PTN has been the first natural ligand identified for RPTPβ/ζ with high affinity (Maeda et al., 1996). It has been proposed that PTN binding to RPTPβ/ζ leads to dimerization of the receptor and loss of its tyrosine phosphatase activity.

This subsequently increases the tyrosine phosphorylation of β-catenin, its dissociation from E-cadherin and its accumulation in the cytoplasm (Meng et al., 2000).

Other downstream targets of the PTN/RPTPβ/ζ signalling are β-adducin (Pariser et al., 2005b) and a member of the Src family, Fyn (Pariser et al., 2005a), all affecting cytoskeletal integrity, adhesion and cell migration.

On the other hand, it has been reported that PTN binding to RPTPβ/ζ leads to dephosphorylation and activation of c-Src kinase, focal adhesion kinase, phosphatidylinositol 3-kinase (PI3K), and Erk1/Erk2 (Souttou et al., 2001b; Polykratis et al., 2005; Hienola et al., 2006; Diamantopoulou et al., 2010; Himburg et al., 2010; Gao et al., 2011; Mikelis et al., 2011).

PTN has been also shown to directly bind $\alpha_v\beta_3$ integrin, which forms a functional complex with RPTPβ/ζ on the cell surface.

In cell lines that express RPTPβ/ζ, the presence or absence of the $\alpha_v\beta_3$ integrin, determines whether PTN stimulates or inhibits cell migration (Mikelis et al., 2009). Through the RPTPβ/ζ/c-Src axis, PTN leads to β3 integrin Tyr773 phosphorylation, which is also required for PTN-induced cell migration (Mikelis et al., 2009).

PTN also binds nucleolin (Take et al., 1994; Said et al., 2005; Koutsioumpa et al., 2012). Through this binding it may inhibit human immunodeficiency virus type 1 (HIV-1) infection (Said et al., 2005). Moreover, cell surface nucleolin mediates PTN-induced endothelial cell migration (Koutsioumpa et al., 2012).

N-syndecan was the first PTN receptor identified (Raulo et al., 1994). PTN binds N-syndecan (Raulo et al., 1994; Kinnunen et al., 1998a; Raulo et al., 2005; Raulo et al., 2006) and induces neurite outgrowth (Raulo et al., 1994; Kinnunen et al., 1998b), other actions related to the nervous system (Nolo et al., 1995; Iseki et al., 2002; Landgraf et al., 2008) and development (Imai et al., 1998; Asahina et al., 2002; Tare et al., 2002). The PTN/N-syndecan pathway has been suggested to involve c-Src activation (Kinnunen et al., 1998b).

ALK is a transmembrane tyrosine kinase (Stoica et al., 2001) suggested to promote PTN-induced cell proliferation (Souttou et al., 2001a; Powers et al., 2002), survival (Bowden et al., 2002) and neuronal differentiation (Souttou et al., 2001a). The PTN/ALK pathway is supposed to activate the Ras-MAPK (Souttou et al., 2001a) or the PI3K-Akt (Bai et al., 2000; Slupianek et al., 2001) signalling pathways. However, there are also studies showing that PTN is not a ligand for ALK (Moog-Lutz et al., 2005; Mathivet et al., 2007). In line with this notion, it has been suggested that instead of PTN directly binding ALK, the latter is indirectly activated by PTN binding to RPTPβ/ζ (Perez-Pinera et al., 2007a).

Two forms of PTN have been suggested to differentially bind PTN receptors; PTN15 has been shown to bind ALK and promote proliferation of glioblastoma cells, whereas PTN18 has been shown to bind RPTPβ/ζ and promote haptotactic migration (Lu et al., 2005).

In a later study, neither of the two PTN forms where able to activate ALK in neuroblastoma and glioblastoma cells (Mathivet et al., 2007). Moreover, based on the fact that PTN binding to αvβ integrin occurs through its C-terminal domain (Mikelis et al., 2011), PTN15 that lacks the C-terminal domain of the full length molecule (Lu et al., 2005) is not expected to bind $\alpha_v\beta_3$.

In fetal alveolar epithelial type II cells, PTN exerts its effects via cross-talk with Wnt/β-catenin signalling (Weng et al., 2009), although this has not been linked to any of the PTN receptors up to date.

Expression

PTN expression (mRNA and protein) has been extensively studied in several cells lines and tissues, under physiological or pathological conditions (reviewed in Böhlen and Kovesdi, 1991; Deuel et al., 2002; Papadimitriou et al., 2009). PTN is expressed in a developmentally regulated manner. It is highly expressed during the embryonic and neonatal periods, while it is poorly expressed at the adult period (Kovesdi et al., 1990; Böhlen and Kovesdi, 1991; Vanderwinden et al., 1992; Rauvala et al., 1994).

PTN is predominantly expressed in brain and neurons (Rauvala, 1989; Tezuka et al., 1990; Silos-Santiago et al., 1996; Chang et al., 2004; Furuta et al., 2004; Hienola et al., 2004; Jung et al., 2004). It is found in the heart (Hampton et al., 1992; Anisimov et al., 2002; Li et al., 2007), kidney (Martin et al., 2006), liver (Asahina et al., 2002), lung (Vanderwinden et al., 1992; Weng et al., 2006), uterus (Milner et al., 1989; Milhiet et al., 1998), testis (Vanderwinden et al., 1992), mammary gland (Ledoux et al., 1997), eye (Roger et al., 2006), bone and teeth (Tezuka et al., 1990;

Erlandsen et al., 2012), and cartilage (Tezuka et al., 1990; Neame et al., 1993; Azizan et al., 2000). PTN has been also found to be expressed in neural (Furuta et al., 2004), mesenchymal (Ma et al., 2005) and embryonic (Soh et al., 2007) stem cells.

High levels of PTN have been detected in several cancers and cell lines derived from these tumours. Examples of such malignancies include breast (Wellstein et al., 1992; Riegel and Wellstein, 1994; Choudhuri et al., 1997; Chang et al., 2007), prostate (Vacherot et al., 1999; Hatziapostolou et al., 2005), cervical (Moon et al., 2003), colon (Souttou et al., 1998; Kong et al., 2012), pancreatic (Weber et al., 2000; Yao et al., 2009), lung (Garver et al., 1993; Jäger et al., 1997; Feng et al., 2010), and ovarian (Nakanishi et al., 1997; Collino et al., 2009; Lee et al., 2012) carcinomas, gliomas (Powers et al., 2002; Ulbricht et al., 2003; Zhang et al., 2004; Grzelinski et al., 2005; Lu et al., 2005; Grzelinski et al., 2006; Ulbricht et al., 2006; Peria et al., 2007; Mikelis et al., 2009), meningiomas (Mailleux et al., 1992), melanomas (Czubayko et al., 1996; Satyamoorthy et al., 2000; Seykora et al., 2003; Wu et al., 2005; Gao et al., 2011), multiple myeloma (Chen et al., 2007; Chen et al., 2009), choriocarcinoma (Schulte et al., 1996), and most cell lines of malignant pediatric tumours (Barthlen et al., 2003).

Localisation

PTN is a secreted protein. It has been also detected in the cell nucleus (Koutsioumpa et al., 2012), but the origin (intracellular versus extracellular) of the nuclear PTN remains unknown.

Function

PTN has got its name due to its pleiotrophic effects (reviewed in Deuel et al., 2002; Jin et al., 2009; Papadimitriou et al., 2009).

Growth and maturation of brain

Neurite outgrowth promoting activity was the first to be acknowledged when PTN was first identified and is considered one of the characteristic PTN functions (Kovesdi et al., 1990; Kretschmer et al., 1991; Rauvala et al., 1994; Amet et al., 2001; Chang et al., 2004; Yanagisawa et al., 2010; Yao et al., 2011). Moreover, PTN is involved in the neurite outgrowth promoting actions of the Y-P30 polypeptide, produced by peripheral blood mononuclear cells of the maternal immune system in pregnancy, during brain development of the embryo (Landgraf et al., 2008), and mediates the neuritogenic activity of embryonic brain-derived chondroitin sulphate/dermatan sulphate hybrid chains (Bao et al., 2005). Levels of PTN expression are significantly regulated by amphetamine administration and PTN seems to have important roles in the modulation of synaptic plasticity (Le Grevès, 2005), the protection of nigrostriatal pathways against amphetamine insult (Gramage et al., 2010b), and limitation of amphetamine-induced neurotoxic and rewarding effects (Gramage et al., 2010a). In the same line, levels of the endogenous expression of PTN affect cognitive deficits and long-term alterations of hippocampal long-term potentiation after adolescent amphetamine treatment (Gramage et al., 2011).

Proliferation-mitogenesis

PTN has been suggested to promote proliferation of endothelial cells (Courty et al., 1991; Fang et al., 1992; Laaroubi et al., 1994), epithelial cells (Fang et al., 1992; Delbé et al., 1995; Souttou et al., 1997; Bernard-Pierrot et al., 2004), prostate cancer LNCaP cells (Hatziapostolou et al., 2005; Hatziapostolou et al., 2006), fibroblasts (Fang et al., 1992; Souttou et al., 1997), osteoblasts (Zhou et al., 1992; Yang et al., 2003), human peripheral blood mononuclear cells (Achour et al., 2001), fetal alveolar epithelial type II cells (Weng et al., 2009) and adult rat hepatocytes (Asahina et al., 2002). Moreover, it mediates the stimulatory effect of hydrogen peroxide (Polytarchou et al., 2005) and FGF2 (Hatziapostolou et al., 2006) on LNCaP cell proliferation. Immobilised PTN has been shown to stimulate proliferation of oligodendrocyte CG-4 and primary progenitor glial 0-2A cells (Rumsby et al., 1999), as well as human umbilical vein and bovine brain capillaries endothelial cells (Papadimitriou et al., 2000). Conversely, it has been proposed to inhibit the proliferation of C6 glioma cells (Parthymou et al., 2008) and the VEGF-induced proliferation of human umbilical vein endothelial cells (Heroult et al., 2004).

Cell migration

PTN has been shown to promote migration of endothelial (Papadimitriou et al., 2001; Souttou et al., 2001b; Ulbricht et al., 2003; Li et al., 2005b; Polykratis et al., 2005; Mikelis et al., 2009), glioblastoma (Ulbricht et al., 2003; Lu et al., 2005; Mikelis et al., 2009), human osteoprogenitor (Yang et al., 2003), human osteoblasts (Li et al., 2005b) and human prostate cancer LNCaP (Hatziapostolou et al., 2005) cells. PTN has been reported to mediate the stimulatory effect of hydrogen peroxide on human endothelial and prostate cancer LNCaP cell migration (Polytarchou et al., 2005; Polytarchou et al., 2009), of eNOS/NO on human endothelial and prostate cancer cell migration (Polytarchou et al., 2009), of aprotinin on human endothelial cell migration (Koutsioumpa et al., 2009) and of FGF2 on LNCaP cell migration (Hatziapostolou et al., 2006). Conversely, it has been suggested to inhibit C6 glioma cell migration (Parthymou et al., 2008) and the VEGF-induced migration of human umbilical vein endothelial cells (Heroult et al., 2004; Polykratis et al., 2004).

Differentiation

PTN has been reported to play a negative role during adipogenesis (Gu et al., 2007; Yi et al., 2011) and to inhibit fetal alveolar epithelial type II cell

differentiation into type I cells (Weng et al., 2009).
Skeletal system
Initially, PTN mRNA was found during development in bone and cartilage progenitors and in dental pulp (Tezuka et al., 1990; Vanderwinden et al., 1992). One biological function that was early attributed to PTN is the promotion of osteoblast attachment to the extracellular bone matrix through its C-terminal domain (Gieffers et al., 1993). It was later shown that bone mass loss observed due to oestrogen deficiency is compensated in transgenic mice over-expressing PTN (Masuda et al., 1997). PTN is prominently expressed in the cell matrices that act as target substrates for bone formation and may play an important role in bone formation, probably by mediating recruitment and attachment of osteoblasts/osteoblast precursors to the appropriate substrates for deposition of new bone (Imai et al., 1998). PTN has the ability to promote adhesion, migration, expansion, and differentiation of human osteoprogenitor cells (Yang et al., 2003) and to regulate periosteal bone formation and resorption in response to four-point bending of right tibias in C57BL/6J mice (Xing et al., 2005), although it was more recently suggested by using PTN knockout mice that it is not a key upstream mediator of the anabolic effects of mechanical loading on the skeleton (Kesavan and Mohan, 2008).
Interestingly, the PTN transgenic mice develop a phenotype characterized by higher bone mineral content and density (Imai et al., 1998) and increased bone growth (Tare et al., 2002); however, a more recent study with targeted PTN over-expression in mouse bone suggests that although PTN mice have advanced bone growth in length and maturation during early stages of bone development, the difference is diminished in later life and the bones become brittle (Li et al., 2005a). On the other hand, although PTN-deficient mice seem to have normal bone formation (Lehmann et al., 2004), they show growth retardation in the weight-bearing bones by two months of age and low bone formation and osteopenia, as well as resistance to immobilization-dependent bone remodelling, during adulthood (Imai et al., 2009).
Injury repair, survival and regeneration in several systems
PTN levels in human serum (Weiss et al., 2009) and rat bone (Petersen et al., 2004) are increased during fracture healing (Petersen et al., 2004; Li et al., 2005a; Weiss et al., 2009).
Treatment with PTN chimaeras after canine carotid artery balloon angioplasty injury resulted in endothelial healing (Brewster et al., 2006). Up-regulation of PTN in heart failure and cardiac ischemia may contribute to the revascularization of the injured heart (Christman et al., 2005; Li et al., 2007). PTN has been reported to facilitate wound healing of injured fetal alveolar epithelial type II cells (Weng et al., 2009).
PTN has been suggested to play a role in the survival of hematopoietic stem cells (Himburg et al., 2010), and the survival and regeneration of dopaminergic neurons (Hida et al., 2003; Jung et al., 2004; Hida et al., 2007). PTN is highly expressed within the injured nerve suggesting a role in peripheral nerve regeneration (Blondet et al., 2005; Jin et al., 2009), in macrophages, astrocytes and endothelial cells after neuronal injury (Takeda et al., 1995; Yeh et al., 1998), in neurons and glial cells after spinal cord injury in rats (Wang et al., 2004), and in denervated nerve and muscle suggestive of a role in axonal regeneration (Mi et al., 2007).
Bacterial growth
PTN has been shown to have bactericidal properties through an unknown, up to date, mechanism (Svensson et al., 2010).
Apoptosis
PTN prevents apoptosis of SW-13 epithelial cells (Bowden et al., 2002) and spermatocytes (Zhang et al., 1999a), and inhibits transforming growth factor β1-induced apoptosis in hepatoma cell lines (Park et al., 2008). Similarly, the functions of PTN/RPTPβ/ζ on human embryonic stem cells seem to depend mainly on its anti-apoptotic effect (Soh et al., 2007). Conversely, PTN potentiates cardiomyocyte apoptosis (Li et al., 2007).

Homology

Homologs. PTN and midkine are the two members of a heparin-binding growth factor family. Common characteristics are reviewed in Muramatsu, 2002; Kadomatsu and Muramatsu, 2004:
- approximately 50% amino acid residue identity,
- basic amino acid rich proteins,
- 10 conserved cysteine residues,
- consist of N- and C-terminal domains,
- C-terminal domain is evolutionary conserved,
- N-terminal domain of the zebrafish midkine and of the human PTN has dominant negative effects.

Orthologs. PTN is a basic amino acid (24%) and cysteine rich protein. Its 10 cysteine residues are conserved in vertebrates and all form disulfide bonds (Hulmes et al., 1993). PTN exhibits high sequence conservation among species (reviewed in Rauvala et al., 2000 and references therein). The PTN C-terminal domain is the most conserved domain evolutionarily (Svensson et al., 2010) (dbSNP, HomoloGene).

Mutations

Note
Mutants
Two SNPs (rs322236 and rs3959914) within the first intron of the gene encoding PTN have been associated with volumetric bone mass density (Zmuda et al., 2011). Polymorphisms in the PTN gene promoter have been also mentioned to affect bone density and might be implicated in osteoporosis (Mencej-Bedrac et al., 2011). Four SNPs and five mutations (COSMIC) have been mentioned, but they have not been linked to expression or function.

Peptides/chimaeras and structure-function relationship
Several PTN peptides and truncated PTN constructs have been studied in an attempt to elucidate the structure/function relationship of PTN:
- The truncated construct P1-40 (dominant negative effector through its ability to form dimers with PTN) has been shown to prevent PTN-induced transformation of the mouse embryonic fibroblast NIH 3T3 cell line and the formation of tumours in the human breast cancer MDA-MB-231 cell line (Zhang et al., 1997).
- Peptides P1-21 and P121-139 have been demonstrated to stimulate endothelial tube formation, proliferation and in vivo angiogenesis (Papadimitriou et al., 2000; Papadimitriou et al., 2001).
- Peptides P9-59 and P60-110 have been reported to induce endothelial cell migration and tube formation, while P9-110 to inhibit migration. All three peptides caused an increase of endothelial adhesion (Polykratis et al., 2004). In a different study, the truncated constructs P9-59 and P60-110 (equivalents of the two out of the three fragments that are produced after MMP-2 cleavage) have been shown to promote or inhibit NIH 3T3 cell proliferation, respectively (Dean et al., 2007).
- The peptide P65-97 has been demonstrated to inhibit the mitogenic, tumourigenic and angiogenic activities of PTN (Hamma-Kourbali et al., 2008).
- The truncated construct P1-110 has been extensively studied. It has been reported to prevent proliferation and tumour formation in NIH 3T3 cells (Bernard-Pierrot et al., 2001), bind ALK, inhibit in vitro and in vivo PTN-induced angiogenesis of endothelial cells, in vitro and in vivo PTN-induced transforming activity of MDA-MB 231 cells (Bernard-Pierrot et al., 2002), to inhibit in vitro and in vivo proliferation of U87 MG glioblastoma cell line, in vivo angiogenesis, and growth and angiogenesis of U87 MG xenografts in nude mice (Dos Santos et al., 2010), and inhibit PTN-induced MDA-MB-231 breast tumour and endothelial cell proliferation and growth (Ducès et al., 2008).
- The peptide P111-136 has been shown to inhibit PTN-mediated PC-3 cell growth and angiogenesis (Hamma-Kourbali et al., 2011).
- The peptide P112-136 has been demonstrated to inhibit PTN binding to $\alpha_v\beta_3$, but not RPTPβ/ζ, inhibit in vivo angiogenesis and the PTN-induced migration and tube formation of human endothelial cells (Mikelis et al., 2011).
- The peptide P122-131 has been reported to inhibit adhesion, proliferation and migration of DU145 and LNCaP cells and in vivo angiogenesis (Diamantopoulou et al., 2010).
- Peptides generated after proteolysis with plasmin were shown to have stimulatory or inhibitory effects on endothelial migration and tube formation, and only stimulatory on cell adhesion (Polykratis et al., 2004).
- Chimaeras of PTN and FGF have been demonstrated to induce re-endothelialization after angioplasty injury (Brewster et al., 2006).

PTN knock-out and PTN-over-expressing mice
PTN-deficient mice are born without major anatomical defects and exhibit enhanced hippocampal long-term potentiation (Amet et al., 2001). However, mice deficient in both PTN and midkine have been shown to exhibit severe auditory deficit (Zou et al., 2006), have high mortality rates within a month of their birth (Muramatsu, 2010) and exhibit female infertility (Muramatsu et al., 2006).
PTN-over-expressing mice exhibit abnormalities in bone formation (Masuda et al., 1997; Hashimoto-Gotoh et al., 2004; Li et al., 2005a) and show decreased hippocampal long-term potentiation (Pavlov et al., 2002).

Implicated in

Various cancers

Note
Enhanced PTN serum levels have been reported from patients with tumour types such as colorectal (Kong et al., 2012), pancreatic (Souttou et al., 1998; Klomp et al., 2002), lung (Jäger et al., 2002; Ostroff et al., 2010), colon (Souttou et al., 1998), testicular (Aigner et al., 2003), multiple myeloma (Yeh et al., 2006; Chen et al., 2007), melanoma (Wu et al., 2005) and a variety of cancers (Soulié et al., 2004) (also see "Expression").
PTN can be potentially used as a marker of the presence of malignancies. It has been shown that patients with pancreatic or colon cancer have elevated serum PTN levels (Souttou et al., 1998; Kong et al., 2012), which drop after successful tumour removal (Souttou et al., 1998). PTN expression is increased in pancreatic cancer tissues compared to inflammatory or normal tissues (Klomp et al., 2002) and may be also linked to the increased perineural invasion and poor prognosis of
pancreatic cancer (Yao et al., 2009). PTN has been also mentioned as a new diagnostic marker for testicular cancer with high sensitivity even in early-stage testicular cancer (Aigner et al., 2003).
The role of PTN in cancer is considered to be both direct by being an autocrine stimulator of tumour cells, and indirect by affecting tumour angiogenesis.
Over-expression of PTN in NIH 3T3 cells leads to anchorage-independent growth in vitro and tumour formation in nude mice in vivo (Chauhan et al., 1993). Human adrenal carcinoma cells expressing PTN acquire autonomous growth in vitro and in vivo (Fang et al., 1992). On the other hand, over-expression of a dominant-negative PTN form in human breast cancer MDA-MB-231 cells decreases their ability to form colonies in soft agar and tumours in nude mice (Zhang et al., 1997). PTN-targeting ribozymes in human melanoma WM852 (Czubayko et al., 1994) or 1205Lu cells (Czubayko et al., 1996; Malerczyk et al., 2005), as well as Colo357 pancreatic cancer (Weber et al., 2000), choriocarcinoma (Schulte et al., 1996) and

glioblastoma (Grzelinski et al., 2005) cells suppress tumour growth in vivo and in vitro. Similarly, a replication-deficient recombinant adenovirus expressing antisense PTN at high efficiency decreases melanoma cell growth in vitro and in vivo (Satyamoorthy et al., 2000), and an RNA-interference PTN gene silencing approach decreases glioblastoma xenografts growth (Grzelinski et al., 2006). Antisense PTN expression in human prostate LNCaP cells decreases cell migration, as well as anchorage-dependent and independent growth in vitro (Hatziapostolou et al., 2005) and abolishes the stimulatory effect of FGF2 (Hatziapostolou et al., 2006) or signalling concentrations of hydrogen peroxide (Polytarchou et al., 2005) in the same cells.

Conversely, antisense PTN expression in rat glioma C6 cells increases cell migration, as well as anchorage-dependent and independent growth in vitro (Parthymou et al., 2008) and increased PTN expression is associated with poor vasculature and better prognosis in neuroblastomas (Calvet et al., 2006). PTN has been also shown to inhibit migration of several glioma cell lines in vitro (Lu et al., 2005; Mikelis et al., 2009).

The role of PTN in tumour angiogenesis has been initially suggested by the observation that culture supernatants derived from PTN transfected human adrenal carcinoma cells (Fang et al., 1992), lung cancer cells (Jäger et al., 1997) or PTN transfected MCF-7 human breast cancer cells (Choudhuri et al., 1997) possess mitogenic activities for endothelial cells. It also increases the angiogenic potential of multiple myeloma (Chen et al., 2009).

Ribozyme targeting of PTN in a human melanoma cell line decreases vessel formation in the primary tumour, as well as metastases (Czubayko et al., 1996), and antisense PTN expression in human prostate LNCaP cells decreases prostate cancer cell-induced angiogenesis in vitro and in vivo (Hatziapostolou et al., 2005).

Conversely, antisense PTN expression in rat glioma C6 cells decreases prostate cancer cell-induced angiogenesis in vitro and in vivo (Parthymou et al., 2008), and PTN seems to act as an angiostatic factor in an in vivo neuroblastoma model that is resistant to irinotecan (Calvet et al., 2006).

Disorders of the central nervous system

Note

PTN has been suggested to provide neuroprotection, prevent drug of abuse-induced neurotoxicity and addiction, and recover the dopaminergic system in Parkinson's disease (Mourlevat et al., 2005; Marchionini et al., 2007; Sotogaku et al., 2007; Ferrario et al., 2008; Moses et al., 2008; Herradón and Ezquerra, 2009; Gramage and Herradón, 2011; Gombash et al., 2012).

PTN has been shown to be deposited in senile plaques in both Alzheimer's disease and Down's syndrome (Wisniewski et al., 1996).

Memory

Note

Mice over-expressing PTN showed attenuated long-term potentiation and were demonstrated to learn faster in behavioural studies (Pavlov et al., 2002). PTN has been reported to inhibit hippocampal long-term potentiation, suggesting a positive role of PTN in memory and learning (del Olmo et al., 2009), and regulation of synaptic plasticity (Lauri et al., 1998; Amet et al., 2001; Pavlov et al., 2006).

Pain

Note

PTN has been presented as a promising candidate to limit neuropathic pain development (Martin et al., 2011).

Auditory function

Note

In mice doubly deficient in the midkine and PTN genes, expression of β-tectorin mRNA requires either midkine or PTN and these mice exhibited very severe auditory deficits. Mice deficient in either midkine or PTN gene were also impaired in their auditory response, but the level of the deficit was generally low or moderate (Zou et al., 2006).

Angiogenesis

Note

Besides the effect of PTN on proliferation and migration of endothelial cells (described in "Function"), PTN has been shown to promote in vitro formation of tube-like structures in collagen gels (Papadimitriou et al., 2001; Souttou et al., 2001b), fibrin gels or matrigel (Papadimitriou et al., 2001), and to stimulate in vivo angiogenesis of the chick embryo chorioallantoic membrane (Papadimitriou et al., 2001; Koutsioumpa et al., 2012), and in matrigel implants in mice (Bernard-Pierrot et al., 2001). Besides a direct effect on endothelial cells, PTN induces transdifferentiation of monocytes into functional endothelial cells (Sharifi et al., 2006; Chen et al., 2009). Conversely, PTN has been reported to inhibit VEGF-induced angiogenesis (Heroult et al., 2004). PTN has also a significant role in cancer angiogenesis (see "Various cancers").

Haematopoiesis

Note

PTN has been recently identified as a new regulator of both haematopoietic stem cells expansion in vitro and regeneration in vivo through PI3K signalling (Himburg et al., 2010). Haematopoietic regeneration seems to be independent of β-catenin and includes cyclin D1 and C/EBPα (Istvanffy et al., 2011).

Cardiovascular conditions

Note

PTN expression has been reported in vascularized

human atherosclerotic plaques (Li et al., 2010b). PTN has been also suggested as a diagnostic marker and a therapeutic target for heart failure (reviewed in Asakura and Kitakaze, 2009).

Inflammatory conditions and autoimmune diseases

Note

Induction of inflammatory cytokines expression by PTN suggests a role of PTN in inflammatory processes (Achour et al., 2008). Moreover, PTN expression is up-regulated by cytokines in inflammatory processes, such as atherosclerosis (Li et al., 2010b) and systemic lupus erythematosus (Ramos et al., 2011), as well as hypoxia (Antoine et al., 2005). Up-regulation of PTN appears to play a role in fibrosis and inflammation during peritoneal injury (Yokoi et al., 2012). PTN has been also reported to be the most highly expressed gene in Peyronie's disease plaque (Magee et al., 2002). PTN up-regulation coincided with clinical recovery in experimental autoimmune encephalomyelitis, an animal model of multiple sclerosis (Liu et al., 1998), and is observed in patients with rheumatoid arthritis (Pufe et al., 2003).

Immune system related conditions

Note

PTN has been demonstrated to induce (HIV-1) expression in peripheral blood mononuclear cells from AIDS patients (M'Bika et al., 2010). Conversely, PTN has been demonstrated to inhibit HIV-1 infection (Said et al., 2005).

Bone and joint diseases

Note

PTN has been identified as a candidate gene for osteoporosis by using a microarray based identification of osteoporosis-related genes in primary culture of human osteoblasts (Trost et al., 2010). Preliminary work has suggested that the PTN gene promoter polymorphism -1227C>T and CT haplotype affects bone density and might be implicated in osteoporosis (Mencej-Bedrac et al., 2011). Two SNPs (rs322236 and rs3959914) in distinct linkage disequilibrium blocks within the first intron of the gene encoding PTN have been associated with volumetric bone mass density (Zmuda et al., 2011).

During fracture healing, PTN is immunolocalised on both osteoblasts and endothelial cells in the well vascularized, newly formed woven bone (Petersen et al., 2004) and recombinant human PTN has chemotactic effects on both human osteoblastic and endothelial cells (Li et al., 2005b). Moreover, fracture healing was impaired in the adult PTN mice and this may be due to inhibitory effects of PTN over-expression on bone morphogenetic protein-2 mediated bone induction (Li et al., 2005b).

PTN is slightly up-regulated in patients with osteoarthritis (Pufe et al., 2003; Pufe et al., 2007; Kaspiris et al., 2010) and has been suggested as a potential therapeutic factor (reviewed in Mentlein, 2007), although evidence is still limited.

To be noted

Note

The authors apologise if they unintentionally omitted the work of some scientists.

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