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Review

PTK7 (PTK7 protein tyrosine kinase 7)

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Identity

Other names: CCK4

HGNC (Hugo): PTK7

Location: 6p21.1

Note: PTK7 is an atypical tyrosine kinase receptor. It belongs to the group of pseudo-kinases as key residues required for catalytic activity are missing in its kinase domain (Mossie et al., 1995; Park et al.,1996; Banga et al., 1997). It represents the only member of its own family. This receptor is involved in many developmental processes as its loss gives rise to severe and lethal defects. PTK7 is implicated in planar cell polarity and in Wnt signaling pathways.

DNA/RNA

Note

The gene of PTK7 spans approximately 85 kb in human and 65 kb in mouse. These two genes shared the same structure and are composed by 20 exons (Jung et al., 2002; Jung et al., 2004).

Description

The PTK7 gene is organized in 20 exons in human and mouse (see figure below). In humans, exon 1 encodes the translation initiation codon and the signal peptide. Exons 2 to 13 encode the extracellular region. The 5'-half of exon 14 encodes the transmembrane region, and the rest of exon 14 and 5'-half of exon 15 encode the juxtamembrane region. The 3'-half of exon 15 and exons 16 to 20 encode the tyrosine kinase domain (Jung et al., 2002).

Transcription

The 883-bp 5'-flanking sequence from the ATG start codon contains a functional promoter. Several canonical binding sites for transcription factors (NFAT, SP1, dEF1, LMO2COM, v-MYB, TCF11, NF1, IK-2, AP4) are present in this sequence and might be important for expression of PTK7 (Jung et al., 2002).

	mRNA	Missing exons	Protein lenght (AA)	Predicted molecular weight (KDa)	Protein Structure	Transcript ensembl reference
Isoform 1	3213 bp	_	1070	118.5	Full length	ENST00000230419
Isoform 2	3093 bp	Exon 10	1030	114	Loss of half of the 6th Ig loop	ENST00000345201
Isoform 3	3045 bp	Exons 8,9, 10	1014	103.7	Loss of the 5th and a part of 6th Ig loops	ENST00000352931
Isoform 4	2823 bp	Exons 12,13	940	112.4	Loss of the 7th Ig loop	ENST00000349241
Isoform 5	2451 bp	Exon 16 to 20	816	90	Loss of the tyrosine kinase domain	ENST00000230418

Moreover, a report showed that expression of PTK7 is regulated by Cdx transcription factors. Indeed, several Cdx response elements in the 5'-flanking sequence of ptk7 have been identified by chromatin immunoprecipitation analysis and activity of these sites have been demonstrated in cultured cells (Savory et al., 2011).

mRNA: Alternative splicing give rise to five PTK7 isoforms in human, which have been described in testis. PTK7-1 is the full length form of PTK7 and the length of its mRNA is 3213 bp. Others isoforms have a loss of one or several exons coding for the extracellular part of the protein (i.e. immunoglobulin loops) and are summarized in the table above (Jung et al., 2002). Shorter PTK7 forms (i.e < 500 AA) have been reported in Ensembl but have not been validated by in vitro experiments.

Protein

Note

PTK7 has a classical RTK structure with an extracellular region, a single transmembrane region and an intracellular tyrosine kinase domain.

Description

The human and mouse PTK7 proteins comprise 1070 and 1062 amino acids, respectively, and share 92.6% identity. The extracellular region is composed by seven immunoglobulin-like domains. Although the kinase domain is catalytically inactive, it is highly evolutionarily conserved during evolution. Three major non-classical sequences have been described: the GXGXXG ATP binding motif is changed in GXSXXG.

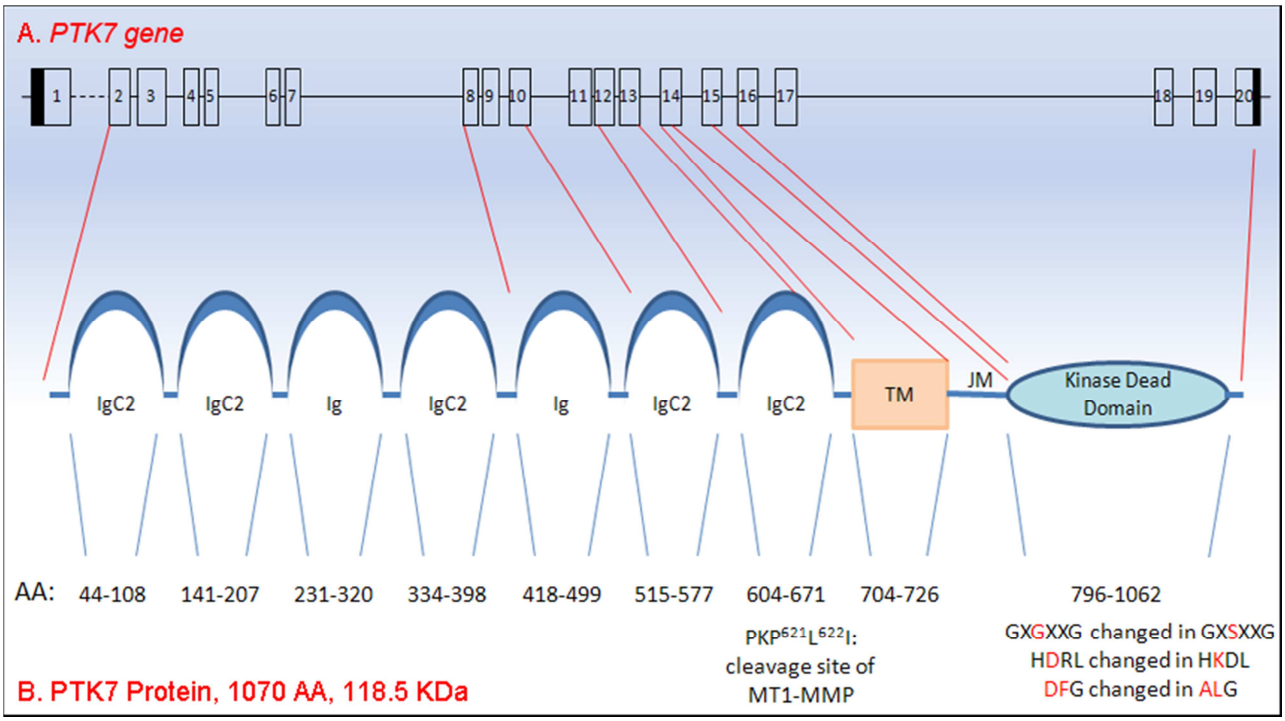
The HDRL motif required for the catalytic proton transfer is changed in a HKDL motif, and the aspartate residue of the DFG motif usually coordinating Mg^{2+}-ATP binding is changed to an uncharged alanine residue (ALG motif) (Jung et al., 2004; Boudeau et al., 2006). No convincing experimental data support yet a catalytic function of the PTK7 tyrosine kinase domain.

Expression

PTK7 is ubiquitously expressed at low level in epithelial, endothelial and hematopoietic tissues. PTK7 is highly expressed in tumoral tissues: colon cancer (Mossie et al., 1995), melanoma (Easty et al., 1997), breast cancer (Speers et al., 2009), acute myeloid leukemia, acute lymphoid leukemia (Müller-Tidow et al., 2004; Prébet et al., 2010).

Localisation

PTK7 is localized at the plasma membrane and has its extracellular domain exposed at the cell surface. It is described that PTK7 is processed by MT1-MPP, a metalloproteinase, that releases a soluble form of PTK7. From in vivo and in vitro studies, it appears that a fine-tuned balance between full length PTK7 and soluble PTK7 is required for normal embryonic development and directional cell migration (Golubkov et al., 2010; Golubkov et al., 2011).



A. Structure and organization of PTK7 gene. Each box represents an exon. **B. Structure and features of PTK7 protein.** Structure and mapping of each immunoglobulin-like loop domains are indicated in the figure. The main features of the protein (i.e cleavage site and non-classical residues in the catalytic domain) are mentioned in the figure. Ig: immunoglobulin loops domain.TM: transmembrane domain. JM: juxtamembrane domain.

Function

The loss of PTK7 protein in mouse leads to a severe and lethal phenotype of neural tube defect closure (craniorachischisis) and abdomen defect closure. Also, PTK7 is implicated in planar cell polarity and in the convergent extension embryonic process (Lu et al., 2004; Yen et al., 2009). Despite the lack of tyrosine kinase activity, PTK7 is involved in epithelial and hematopoietic cell migration. PTK7 is able to interact with VEGFR1 and is implicated into angiogenesis (Shin et al., 2008; Lee et al., 2011). In term of signaling, PTK7 is able to bind to β-catenin and Dsh proteins (Shnitsar and Borchers, 2008). The formation of a tripartite complex Dsh-Rack1-Fz7 places PTK7 as an actor of non-canonical Wnt pathway (Wehner et al., 2011). Interaction with β-catenin suggests that PTK7 is also involved in canonical Wnt pathway (Puppo et al., 2011). However, the role of PTK7 as activator or inhibitor of Wnt canonical signaling is still controversial (Peradziryi et al., 2011).
In Drosophila, PTK7 (also called OTK) forms a protein complex with members of the Plexin family proteins. Also, OTK is apparently also involved in the Plexin-Semaphorin pathway (Wagner et al., 2010).

Homology

The extracellular part show similarities with adhesion molecules of the immunoglobulin superfamily due to the presence of immunoglobulin loops domains. Phylogenetic study showed that among the RTKs of the immunoglobulin superfamily, ptk7 and musk genes have derived very early during evolution and have created an independent branch probably endowed with particular functions. Indeed, Musk shows the highest identity sequence with PTK7 (42%) when the extracellular domains are compared (Grassot et al., 2006).

Mutations

Note
Some mutations have been found in human ptk7, but to date none of them have been correlated to any diseases. However, frequent overexpression of the receptor is observed in solid and haematological cancers.

Implicated in

Development

Note
PTK7 plays a major role in planar cell polarity and convergent extension processes.

Disease
Gene-trapped PTK7 leads to neural tube and abdomen closure defects associated with several developmental abnormalities as polydactyly, smaller kidney and open eyes in the mouse (Lu et al., 2004).

Prognosis
Embryonic lethal.

Oncogenesis

Note
PTK7 is highly expressed in tumoral tissues.

Disease
Colon cancer, melanoma, breast cancer, acute myeloid leukemia, acute lymphoid leukemia.

Prognosis
Controversial studies have been reported. In melanoma, loss of PTK7 expression was correlated with advanced stage of disease (Easty et al.,1997). In other cancer, expression of PTK7 is linked with adverse prognosis and increased resistance to chemotherapeutic drugs (AML) (Prébet et al., 2010), and breast cancer (Speers et al., 2009).

Hybrid/Mutated gene
Not described.

Angiogenesis

Note
PTK7 crosstalks with active receptor tyrosine kinase family members such as VEGFR1, and regulates migration of endothelial cells. In endothelial cells, VEGF-A triggers VEGFR1 phosphorylation and association with PTK7. This interaction is needed for optimal phosphorylation and activation of downstream components of VEGFR1 signaling, including AKT and FAK that are required for the angiogenic process (Lee et al., 2011). Accordingly, downregulation of PTK7 expression in vitro and in vivo leads to a decreased angiogenesis (Shin et al., 2008). An anti-angiogenic effect can be obtained using a soluble recombinant form of PTK7, suggesting a dominant-negative effect on the extracellular domain.

Wnt pathways

Note
PTK7 is a key protein of Wnt pathway regulation. In one hand, PTK7 is involved in non-canonical PCP Wnt pathway, through a direct interaction with Dishevelled (Dsh) and Rack1. In this pathway, PTK7 probably induces a Rho/Rac/JNK signalling cascade that controls actin cytoskeleton remodelling (Montcouquiol et al., 2006). On the other hand, PTK7 interacts directly by its tyrosine kinase domain with β-catenin, which is a key protein of the canonical Wnt pathway. PTK7 deficient cells exhibit weakened β-catenin/T-cell factor transcriptional activity upon Wnt3a stimulation (Puppo et al., 2011). However, as Rack1 is known to antagonize canonical Wnt pathways, other authors suggest that the PTK7/Rack1 complex can potentially repress the canonical Wnt signaling (Peradziryi et al., 2012). Further studies will be necessary to highlight how PTK7 crosstalks between canonical and non-canonical Wnt pathways.

Disease

Wnt pathway is a major signaling pathway during development and is involved in many cellular mechanisms including carcinogenesis.

To be noted

Note

No ligand of PTK7 receptor has been yet identified. Despite the lack of tyrosine kinase activity, PTK7 appears to have a role in signal transduction and emerges as an important regulator of VEGFR1 and Wnt pathways (Lhoumeau et al., 2011).

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