

Gene Section

Review

ENPP2 (ectonucleotide pyrophosphatase/phosphodiesterase 2)

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Identity

Hugo: ENPP2

Other names: Autotaxin; ATX; NPP2; PD1alpha; lysophospholipase D; PDNP2

Location: 8q24.12

Local order: Telomeric to NOV (nephroblastoma overexpressed gene), centromeric to TAF2; colocalized with pseudogene CYCSP23.

DNA/RNA

Note: mRNA length 3276 or 3120 bp, depending upon alternate splicing.

Description

The ENPP2 gene is 81,754 bp in length and is composed of 26 exons. Part of exon 1 and 26 are untranslated (UTR); translation extends from the remainder of exon 1 through the proximal portion of

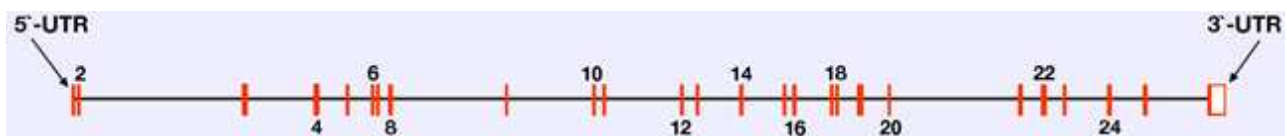
exon 26; however, there is a 152 bp exon (exon 12) that is alternatively spliced and is included primarily in neurally derived tissues.

Transcription

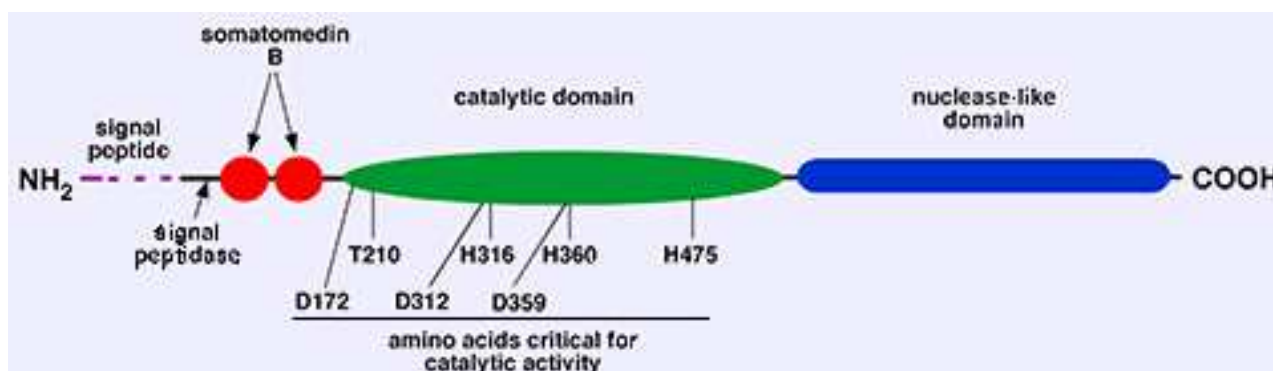
The mRNA for ENPP2 is 3276 bp with exon 12 and 3120 bp without it. The ENPP2 promoter is reported to have four SP1 sites as well as binding sites for NFAT and NF-kappaB but no TATA or CAAT boxes. The only transcription factor that has been proven to increase ENPP2 protein expression is NFATC2/NFAT1, after release of alpha6beta4 from hemidesmosomes in a breast cancer cell line. A number of growth factors have been found to stimulate ENPP2 protein expression, while several inflammatory cytokines have been reported to inhibit expression.

Pseudogene

CYCSP23



ENPP2 Gene: Intron-exon organization of ENPP2.



ENPP2 Protein (NPP2/ATX): Organization of domains and other critical elements within ENPP2.

Protein

Description

The ENPP2 protein, NPP2 or ATX, is an N-glycosylated member of the ecto-nucleotide pyrophosphatase and phosphodiesterase (NPP) family of proteins. The NPP2 precursor contains 915 amino acids, 105.2 KDa; and an alternately spliced variant is 863 amino acids, 99.0 KDa. The amino terminal signal peptide sequence is cleaved at a signal peptidase site between G27 and F28 to yield a secreted protein that contains 888/836 amino acids, 102.3/96.9 KDa. NPP2 contains up to 3 ASN-linked glycosylation sites that appear to be required for secretion as well as for stabilization of its active conformation.

Expression

NPP2 is expressed in many tissues during development, but it is critical for blood vessel maturation and neurogenesis. Certain inflammatory cytokines and the tumor suppressor CST6 downregulate ENPP2 expression, and some of the NPP2 products exert a negative feedback on its expression. Conversely, a number of growth factors as well as EBV infection (in Hodgkin's lymphoma) upregulate ENPP2 expression. Disruption of hemidesmosomes in breast cancer cells releases alpha6beta4, which initiates a signaling cascade that culminates in the activation of the transcription factor NFAT1, which binds to the ENPP2 promoter to upregulate protein expression. Upregulation of ENPP2 has been reported in a number of aggressive tumors, including glioblastoma, undifferentiated anaplastic thyroid carcinoma, invasive breast carcinoma, and metastatic hepatocellular carcinoma.

In adults, NPP2 is the major source of serum and plasma lysophospholipase D activity. It is also highly expressed in brain, kidney, liver, ovary, small intestine, and placenta, and is present in many other tissues.

Function

NPP2 is a Type 2 nucleotide pyrophosphatase and phosphodiesterase that also has ATPase activity. In addition, NPP2 is the major source of serum and

plasma lysophospholipase D activity, hydrolyzing lysophosphatidylcholine into lysophosphatidic acid as well as cyclic phosphatidic acid. NPP2 also hydrolyzes sphingosylphosphorylcholine into sphingosine-1-phosphate; however, NPP2 is not a major source of sphingosine-1-phosphate in plasma. The production of lysophosphatidic acid is thought to account for many of the physiological and pathological roles of ENPP2.

Both enzymatic activities of NPP2 share a common catalytic domain. Like other members of the NPP family, NPP2 is a metallo-enzyme with binding sites for 2 metal atoms coordinated by three critical histidines (H316, H360, and H475) and associated aspartates (D172, D312, and D359). T210 is nucleotidylated during the nucleotide pyrophosphatase/phosphodiesterase reaction and is essential for hydrolysis of substrate during the lysophospholipase D reaction as well.

Homology

NPP2 is a member of the nucleotide pyrophosphatase and phosphodiesterase family, which includes ENPP1 (PC1) and ENPP3 (B10). Although the catalytic domain is highly conserved within this family of proteins, only NPP2 possesses lysophospholipase D activity.

Mutations

Note: There are a number of single nucleotide polymorphisms (SNPs) that have been reported within the ENPP2 gene but none are yet reported to be associated with altered phenotype. However, knockout of ENPP2 is lethal in mice (approximately E12), therefore mutations associated with loss of function might be lethal.

Implicated in

Various cancers

Disease

Overexpression of the ENPP2 protein has been associated with tumor cell motility and invasion, tumor growth and metastasis, and blood vessel formation.

Prognosis

ENPP2 is over-expressed in poorly differentiated non-small cell lung carcinomas and invasive and metastatic hepatocellular carcinoma. In thyroid carcinomas, ENPP2 expression was found to be higher in undifferentiated anaplastic thyroid carcinoma cell lines and tissues than in follicular thyroid carcinomas or goiters. When glioblastoma multiforme cells were collected from tumor cores vs. areas of white matter invasion, ENPP2 was found to be overexpressed predominantly at the invasive front.

Oncogenesis

Upregulation of NPP2 expression appears to be associated with cancer progression rather than with oncogenesis. Transfection of ENPP2 cDNA into mouse fibroblast cell lines (NIH3T3 clone7) did not result in tumorigenic cell lines, but transfection into Ras-transformed fibroblasts resulted in rapidly growing, hematogenous, highly metastatic tumors. NPP2 expression was found in Hodgkin's lymphoma cells as well as in CD30+ anaplastic large-cell lymphomas. In the Hodgkin's lymphomas, EBV infection was correlated to induction of ENPP2 expression ($P = 0.006$).

Transfection of the tumor suppressor CST6 into MDA-MB-435 cells resulted in down-regulation of ENPP2. In contrast, down regulation of ENPP2 by specific siRNAs resulted in down-regulation of the tumor suppressors, thrombospondin-1 and thrombospondin-2 (THBS1 and THBS2, respectively).

Diabetes

Disease

NPP2 expression is highly upregulated during adipocyte differentiation and its product, lysophosphatidic acid, stimulates proliferation in preadipocytes. In genetically obese, diabetic mice, NPP2 expression was increased in adipose tissue compared to their lean siblings. This is a possible model for type 2 diabetes, which has a strong genetic component.

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