Atlas of Genetics and Cytogenetics
in Oncology and Haematology

OPEN ACCESS JOURNAL AT INIST-CNRS

Gene Section
Review

TYMP (thymidine phosphorylase)

Irene V Bijnsdorp, Godefridus J Peters

Department of Medical Oncology, VU University Medical Center, Amsterdam, The Netherlands (IVB, GJP)

Published in Atlas Database: March 2010

Online updated version : http://AtlasGeneticsOncology.org/Genes/TYMPID40397ch22q13.html
DOI: 10.4267/2042/44924

Identity

Other names: ECGF1, hPD-ECGF, MNGIE, PDECGF, TP

HGNC (Hugo): TYMP

Location: 22q13.33

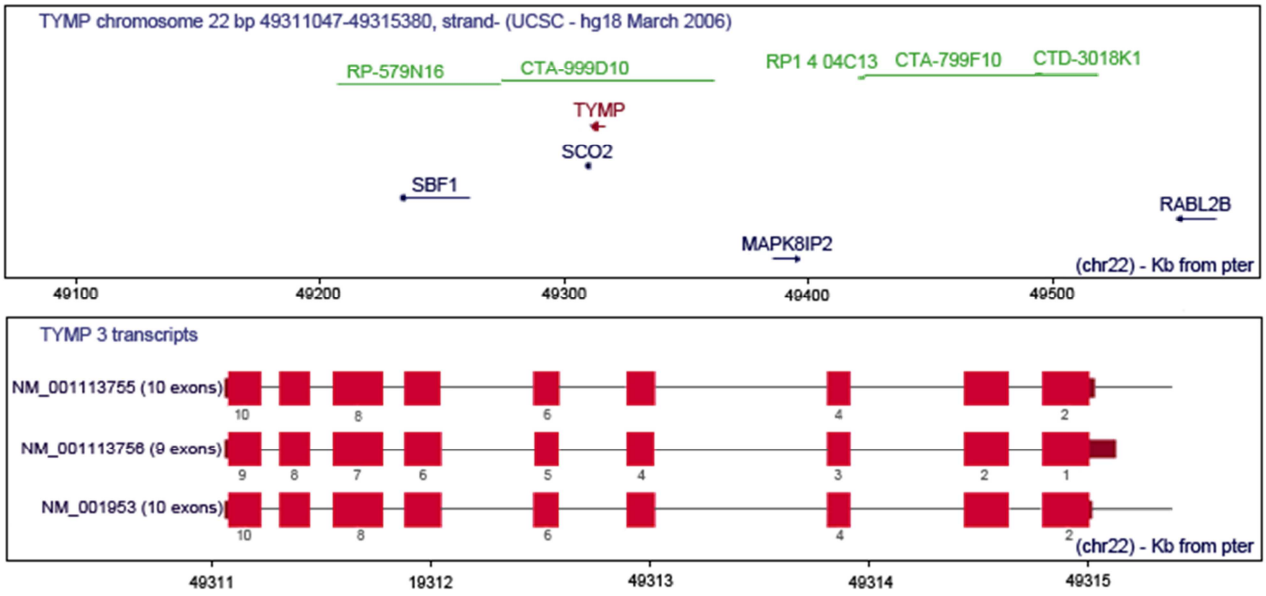
DNA/RNA

Note

The TP gene encodes an angiogenic factor which promotes angiogenesis both in vitro and in vivo and is involved in nucleotide synthesis and thymidine phosphorolysis.

Description

Thymidine phosphorylase is located at chromosome 22 in the region of q13.33. cDNA is approximately 1.8 kb long, consisting of 10 exons in a 4.3 kb region (Hagiwara et al., 1991; Stenman et al., 1992). TP was first cloned and sequenced in 1989 (Ishikawa et al., 1989). The nucleic acid sequence of TP is highly conserved, the human TP shares 39% sequence identity with that of E. coli (Barton et al., 1992).



TYMP is located on chromosome 22 of which 3 transcripts have been identified.

Transcription

The promoter region of the TP gene has no TATA box or CCAAT box, but has a high G-C content and seven copies of the SP-1 binding site upstream from the transcription start site.
Exact TP gene regulation is unknown, but has been described to be (indirectly) regulated by NFkB, TNF-alpha and IFN-gamma (Waguri et al., 1997; Zhu et al., 2002; Zhu et al., 2003; Eda et al., 1993; de Bruin et al., 2004).

Protein

Note
Thymidine phosphorylase was first identified as the platelet-derived endothelial cell growth factor, because it was related to endothelial cell growth (Miyazono et al., 1987; Ishikawa et al., 1989). Later on, it was found that it was identical to thymidine phosphorylase (Furukawa et al., 1992). Thymidine phosphorylase (TP) is the most correct name to refer to this protein, since it catalyzes the phopshorolysis of thymidine to thymine. TP undergoes limited post-translational modification and is not glycosylated. Covalent linkage between serine residues of TP and phosphate groups of nucleotides has been observed, which may facilitate secretion of the protein (Usuki et al., 1991). However, TP does not contain a classical secretion signal (Ishikawa et al., 1989). TP is a dimer, consisting of two identical subunits that are non-covalently associated (Desgranges et al., 1981) with its dimeric molecular mass ranging from 90 kD in Escherichia coli to 110 kD in mammals (Schwartz, 1978; Desgranges et al., 1981).

Description

TP protein does not contain a known receptor binding region or a secretion signal (Ishikawa et al., 1989). It is implicated in nucleotide synthesis and degradation of thymidine. TP is also implicated in angiogenesis (reviewed in de Bruin et al., 2006; Liekens et al., 2007; Bronckaers et al., 2009).

Expression

TP is highly expressed in liver tissues. Furthermore, TP is often overexpressed in tumor sites and is involved in inflammatory diseases, such as rheumatoid arthritis.

Localisation

TP is expressed in the cytoplasm and the nucleus (Fox et al., 1995).

Function

TP catalyzes the phosphorolysis of thymidine (TdR) to thymine and 2-deoxy-alpha-D-ribose 1-phosphate (dR-1-P). TP can also catalyze the formation of thymidine from thymine and dR-1-P. TP also catalyzes the phosphorolysis of deoxyuridine to uracil and dR-1-P. TP also has deoxyribosyl transferase activity by which the deoxyribosyl moiety is transferred from a pyrimidine nucleoside to another pyrimidine base. Subsequently a new pyrimidine nucleoside is formed.
The sugars that are formed by degradation of thymidine are thought to play a role in the induction of angiogenesis. Deoxyribose-1-P can be converted to deoxyribose-5-phosphate or degraded to deoxyribose. Deoxyribose can be secreted, and possibly attract endothelial cells to form new blood vessels (reviewed in de Bruin et al., 2006; Liekens et al., 2007; Bronckaers et al., 2009). TP in some cancer cells can also increase their invasive potential, although the exact mechanism remains unclear.
TP can also activate or inactivate several pyrimidines or pyrimidine nucleoside analogs with antiviral and antitumoral activity, such as inactivation of trifluorothymidine (TFT) (Heidelberger et al., 1964) and 5-fluoro-2'-deoxyruidine (van Laar et al., 1998), or activation of 5-fluorouracil (5-FU) (Schwartz et al., 1995) and 5-fluoro-5'-deoxyuridine (5'DFUR).

Homology

The TYMP gene is conserved in chimpanzee, mouse, rat, and zebrafish.

Mutations

Note
Mutations in this gene have been associated with mitochondrial neurogastrointestinal encephalomyopathy (MNGIE). Multiple alternatively spliced variants, encoding the same protein, have been identified.

Implicated in

Various cancer

Note
TP in tumor sites can be expressed in the cancer cells, in the most malignant cells, tumor stromal cells (such as macrophages) or in the invasive part of the tumor (van Triest et al., 1999). A high TP expression and activity have been related to a poor outcome and increased angiogenesis. The TP gene is regulated by many other factors that are implicated in cancer, such as NFkB (de Bruin et al., 2004). TP regulates the expression of IL-8, and possibly also that of other genes, although the exact mechanism of this regulation is still unclear (Brown et al., 2000; Bijnsdorp et al., 2008). The high TP activity in the tumor can selectively activate the 5FU prodrug 5'-deoxy-5-fluorouridine to 5FU. 5'deoxy-5-fluorouridine is an intermediate of the oral 5FU prodrug Capecitabine (Xeloda) (de Bruin et al., 2006). On the other hand TP can inactivate the fluoropyrimidine trifluorothymidine (TFT), which is registered as the antiviral drug Viroptic® (De Clercq, 2004). An inhibitor of TP, TPI, will prevent inactivation of TFT. TAS-102 is a combination of TFT and TPI (in a molar ratio of 1:0.5) which is developed as an anticancer drug (Temmink et al., 2007).

Disease
Gastrointestinal tumors (Fox et al., 1995; Yoshikawa et al., 1999; Kimura et al., 2002; Takebayashi et al., 1996), breast cancer (Moghaddam et al., 1995), bladder cancer (O'Brien et al., 1996).

Prognosis
High expression is often related to a poor prognosis, an increased microvessel density and increased metastasis.

Abnormal protein
No fusion protein has been described.

Rheumatoid arthritis

Note
Elevated levels of (circulating) PD-ECGF (TP) were found in rheumatoid arthritis patients (Asai et al., 1993). In the sera and synovial fluids of patients suffering from rheumatoid arthritis PD-ECGF (TP) was detected at high levels (Asai et al., 1993). In addition, there was a significant positive correlation between PD-ECGF (TP) levels in synovial fluid and in serum (Asai et al., 1993). The elevated PD-ECGF (TP) levels presumably arise through induction of PD-ECGF (TP) in synoviocytes, resulting from aberrant production of cytokines like TNF-alpha and IL-1 (Waguri et al., 1997).

Atherosclerosis

Note
TP is expressed in atherosclerosis. Macrophages, foam cells and giant cells from both aortic and coronary plaques expressed TP, suggesting that TP may play a role in the pathogenesis of atherosclerosis (Boyle et al., 2000).

Psoriasis

Note
Increased PD-ECGF (TP) mRNA and immunoreactivity were found in lesional psoriasis compared to the non-lesional skin (Creamer et al., 1997). In another study it was reported that the thymidine phosphorylase activity was twenty-fold higher in psoriatic lesions than in normal skin (Hammerberg et al., 1991).

Inflammatory bowel disease

Note
In inflammatory bowel disease, TP has been found to be overexpressed, predominantly in macrophages and fibroblasts of the inflamed colonic mucosa. The grade of expression augmented with an increasing grade of inflammation. In addition, TP was found in the endothelial cells of the inflamed colonic mucosa (Giatromanolaki et al., 2003; Saito et al., 2003).

Chronic glomerulonephritis

Note
TP is upregulated in chronic glomerulonephritis (a renal disease characterized by inflammation of the glomeruli) where it probably plays a critical role in the progression of interstitial fibrosis (Wang et al., 2006).

Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE)

Note
An autosomal recessive disorder involving DNA alterations (Bardosi et al., 1987). Gene mutations in the TP gene include missense, splice sites microdeletions and single nucleotide insertions (Spinazzola et al., 2002; Nishino et al., 2000). These mutations are associated with a severe reduction in TP activity. This leads to increased thymidine plasma levels, and increased deoxyuridine levels (which is also a substrate for TP).

Prognosis
Not determined.

References

HEIDELBERGER C, ANDERSON SW. FLUORINATED PYRIMIDINES. XXI. THE TUMOR-INHIBITORY ACTIVITY OF 5-TRIFLUOROMETHYL-2'-DEOXYURIDINE. Cancer Res. 1964 Dec;24:1979-85

Schwartz M. Thymidine phosphorylase from Escherichia coli. Methods Enzymol. 1978;51:442-5

Desgranges C, Razaka G, Rabaud M, Bricaud H. Catabolism of thymidine in human blood platelets: purification and properties of thymidine phosphorylase. Biochim Biophys Acta. 1981 Jul 27;654(2):211-8

Bardosi A, Creutzfeldt W, DiMauro S, Felgenhauer K, Friede RL, Goebel HH, Kohlschütter A, Mayer G, Rahlf G, Servidei S. Myo-, neuro-, gastrointestinal encephalopathy (MNGIE syndrome) due to partial deficiency of cytochrome-c-oxidase. A new mitochondrial multisystem disorder. Acta Neuropathol. 1987;74(3):248-58

Miyazono K, Okabe T, Urabe A, Takaku F, Heldin CH. Purification and properties of an endothelial cell growth factor from human platelets. J Biol Chem. 1987 Mar 25;262(9):4098-103

Ishikawa F, Miyazono K, Hellman U, Drexler H, Wernstedt C, Hagiwara K, Usuki K, Takaku F, Risau W, Heldin CH. Identification of angiogenic activity and the cloning and expression of platelet-derived endothelial cell growth factor. Nature. 1989 Apr 13;338(6216):557-62

Hagiwara K, Stenman G, Honda H, Sahlin P, Andersson A, Miyazono K, Heldin CH, Ishikawa F, Takaku F. Organization and chromosomal localization of the human platelet-derived endothelial cell growth factor gene. Mol Cell Biol. 1991 Apr;11(4):2125-32

Hammerberg C, Fisher GJ, Voorhees JJ, Cooper KD. Elevated thymidine phosphorylase activity in psoriatic lesions accounts for the apparent presence of an epidermal "growth inhibitor," but is not in itself growth inhibitory. J Invest Dermatol. 1991 Aug;97(2):286-90

Usuki K, Miyazono K, Heldin CH. Covalent linkage between nucleotides and platelet-derived endothelial cell

growth factor. J Biol Chem. 1991 Oct 25;266(30):20525-31

Barton GJ, Ponting CP, Spraggon G, Finnis C, Sleep D. Human platelet-derived endothelial cell growth factor is homologous to Escherichia coli thymidine phosphorylase. Protein Sci. 1992 May;1(5):688-90

Furukawa T, Yoshimura A, Sumizawa T, Haraguchi M, Akiyama S, Fukui K, Ishizawa M, Yamada Y. Angiogenic factor. Nature. 1992 Apr 23;356(6371):668

Stenman G, Sahlin P, Dumanski JP, Hagiwara K, Ishikawa F, Miyazono K, Collins VP, Heldin CH. Regional localization of the human platelet-derived endothelial cell growth factor (ECGF1) gene to chromosome 22q13. Cytogenet Cell Genet. 1992;59(1):22-3

Asai K, Hirano T, Matsukawa K, Kusada J, Takeuchi M, Otsuka T, Matsui N, Kato T. High concentrations of immunoreactive gliostatin/platelet-derived endothelial cell growth factor in synovial fluid and serum of rheumatoid arthritis. Clin Chim Acta. 1993 Sep 17;218(1):1-4

Eda H, Fujimoto K, Watanabe S, Ura M, Hino A, Tanaka Y, Wada K, Ishitsuka H. Cytokines induce thymidine phosphorylase expression in tumor cells and make them more susceptible to 5'-deoxy-5-fluorouridine. Cancer Chemother Pharmacol. 1993;32(5):333-8

Takeuchi M, Otsuka T, Matsui N, Asai K, Hirano T, Moriyama A, Isobe I, Eksioglu YZ, Matsukawa K, Kato T. Aberrant production of gliostatin/platelet-derived endothelial cell growth factor in rheumatoid synovium. Arthritis Rheum. 1994 May;37(5):662-72

Fox SB, Moghaddam A, Westwood M, Turley H, Bicknell R, Gatter KC, Harris AL. Platelet-derived endothelial cell growth factor/thymidine phosphorylase expression in normal tissues: an immunohistochemical study. J Pathol. 1995 Jun;176(2):183-90

Moghaddam A, Zhang HT, Fan TP, Hu DE, Lees VC, Turley H, Fox SB, Gatter KC, Harris AL, Bicknell R. Thymidine phosphorylase is angiogenic and promotes tumor growth. Proc Natl Acad Sci U S A. 1995 Feb 14;92(4):998-1002

Schwartz EL, Baptiste N, Wadler S, Makower D. Thymidine phosphorylase mediates the sensitivity of human colon carcinoma cells to 5-fluorouracil. J Biol Chem. 1995 Aug 11;270(32):19073-7

O'Brien TS, Fox SB, Dickinson AJ, Turley H, Westwood M, Moghaddam A, Gatter KC, Bicknell R, Harris AL. Expression of the angiogenic factor thymidine phosphorylase/platelet-derived endothelial cell growth factor in primary bladder cancers. Cancer Res. 1996 Oct 15;56(20):4799-804

Takebayashi Y, Yamada K, Miyadera K, Sumizawa T, Furukawa T, Kinoshita F, Aoki D, Okumura H, Yamada Y, Akiyama S, Aikou T. The activity and expression of thymidine phosphorylase in human solid tumours. Eur J Cancer. 1996 Jun;32A(7):1227-32

Creamer D, Jaggar R, Allen M, Bicknell R, Barker J. Overexpression of the angiogenic factor platelet-derived endothelial cell growth factor/thymidine phosphorylase in psoriatic epidermis. Br J Dermatol. 1997 Dec;137(6):851-5

Waguri Y, Otsuka T, Sugimura I, Matsui N, Asai K, Moriyama A, Kato T. Gliostatin/platelet-derived endothelial cell growth factor as a clinical marker of rheumatoid arthritis and its regulation in fibroblast-like synoviocytes. Br J Rheumatol. 1997 Mar;36(3):315-21

van Laar JA, Rustum YM, Ackland SP, van Groeningen CJ, Peters GJ. Comparison of 5-fluoro-2'-deoxyuridine with 5-fluorouracil and their role in the treatment of colorectal cancer. Eur J Cancer. 1998 Feb;34(3):296-306

Yoshikawa T, Suzuki K, Kobayashi O, Sairenji M, Motohashi H, Tsuburaya A, Nakamura Y, Shimizu A, Yanoma S, Noguchi Y. Thymidine phosphorylase/platelet-derived endothelial cell growth factor is upregulated in advanced solid types of gastric cancer. Br J Cancer. 1999 Mar;79(7-8):1145-50

Boyle JJ, Wilson B, Bicknell R, Harrower S, Weissberg PL, Fan TP. Expression of angiogenic factor thymidine phosphorylase and angiogenesis in human atherosclerosis. J Pathol. 2000 Oct;192(2):234-42

Brown NS, Jones A, Fujiyama C, Harris AL, Bicknell R. Thymidine phosphorylase induces carcinoma cell oxidative stress and promotes secretion of angiogenic factors. Cancer Res. 2000 Nov 15;60(22):6298-302

Nishino I, Spinazzola A, Papadimitriou A, Hammans S, Steiner I, Hahn CD, Connolly AM, Verloes A, Guimarães J, Maillard I, Hamano H, Donati MA, Semrad CE, Russell JA, Andreu AL, Hadjigeorgiou GM, Vu TH, Tadesse S, Nygaard TG, Nonaka I, Hirano I, Bonilla E, Rowland LP, DiMauro S, Hirano M. Mitochondrial neurogastrointestinal encephalomyopathy: an autosomal recessive disorder due to thymidine phosphorylase mutations. Ann Neurol. 2000 Jun;47(6):792-800

van Triest B, Pinedo HM, Blaauwgeers JL, van Diest PJ, Schoenmakers PS, Voorn DA, Smid K, Hoekman K, Hoitsma HF, Peters GJ. Prognostic role of thymidylate synthase, thymidine phosphorylase/platelet-derived endothelial cell growth factor, and proliferation markers in colorectal cancer. Clin Cancer Res. 2000 Mar;6(3):1063-72

Kimura H, Konishi K, Kaji M, Maeda K, Yabushita K, Miwa A. Correlation between expression levels of thymidine phosphorylase (dThdPase) and clinical features in human gastric carcinoma. Hepatogastroenterology. 2002 May-Jun;49(45):882-6

Spinazzola A, Marti R, Nishino I, Andreu AL, Naini A, Tadesse S, Pela I, Zammarchi E, Donati MA, Oliver JA, Hirano M. Altered thymidine metabolism due to defects of thymidine phosphorylase. J Biol Chem. 2002 Feb 8;277(6):4128-33

Zhu GH, Lenzi M, Schwartz EL. The Sp1 transcription factor contributes to the tumor necrosis factor-induced expression of the angiogenic factor thymidine phosphorylase in human colon carcinoma cells. Oncogene. 2002 Dec 5;21(55):8477-85

Giatromanolaki A, Sivridis E, Maltezos E, Papazoglou D, Simopoulos C, Gatter KC, Harris AL, Koukourakis MI. Hypoxia inducible factor 1alpha and 2alpha overexpression in inflammatory bowel disease. J Clin Pathol. 2003 Mar;56(3):209-13

Saito S, Tsuno NH, Sunami E, Hori N, Kitayama J, Kazama S, Okaji Y, Kawai K, Kanazawa T, Watanabe T, Shibata Y, Nagawa H. Expression of platelet-derived endothelial cell growth factor in inflammatory bowel disease. J Gastroenterol. 2003;38(3):229-37

Zhu GH, Schwartz EL. Expression of the angiogenic factor thymidine phosphorylase in THP-1 monocytes: induction by autocrine tumor necrosis factor-alpha and inhibition by aspirin. Mol Pharmacol. 2003 Nov;64(5):1251-8

de Bruin M, Peters GJ, Oerlemans R, Assaraf YG, Masterson AJ, Adema AD, Dijkmans BA, Pinedo HM, Jansen G. Sulfasalazine down-regulates the expression of the angiogenic factors platelet-derived endothelial cell growth factor/thymidine phosphorylase and interleukin-8 in human monocytic-macrophage THP1 and U937 cells. Mol Pharmacol. 2004 Oct;66(4):1054-60

De Clercq E. Antiviral drugs in current clinical use. J Clin Virol. 2004 Jun;30(2):115-33

de Bruin M, Temmink OH, Hoekman K, Pinedo H, Peters GJ.. Role of platelet derived endothelial cell growth factor/ thymidine phosphorylase in health and disease. Cancer Therapy. 2006;4:99-124. (REVIEW)

Wang EH, Goh YB, Moon IS, Park CH, Lee KH, Kang SH, Kang CS, Choi YJ. Upregulation of thymidine phosphorylase in

chronic glomerulonephritis and its role in tubulointerstitial injury. Nephron Clin Pract. 2006;102(3-4):c133-42

Liekens S, Bronckaers A, Pérez-Pérez MJ, Balzarini J. Targeting platelet-derived endothelial cell growth factor/thymidine phosphorylase for cancer therapy. Biochem Pharmacol. 2007 Dec 3;74(11):1555-67

Temmink OH, Emura T, de Bruin M, Fukushima M, Peters GJ. Therapeutic potential of the dual-targeted TAS-102 formulation in the treatment of gastrointestinal malignancies. Cancer Sci. 2007 Jun;98(6):779-89

Bijnsdorp IV, de Bruin M, Laan AC, Fukushima M, Peters GJ. The role of platelet-derived endothelial cell growth factor/thymidine phosphorylase in tumor behavior. Nucleosides Nucleotides Nucleic Acids. 2008 Jun;27(6):681-91

Bronckaers A, Gago F, Balzarini J, Liekens S. The dual role of thymidine phosphorylase in cancer development and chemotherapy. Med Res Rev. 2009 Nov;29(6):903-53

This article should be referenced as such:

Bijnsdorp IV, Peters GJ. TYMP (thymidine phosphorylase). Atlas Genet Cytogenet Oncol Haematol. 2010; 14(12):1170-1174.