TYMP (thymidine phosphorylase)

Irene V Bijnsdorp, Godefridus J Peters

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

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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; Edu 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 phosphorolysis 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 kDa in Escherichia coli to 110 kDa in mammals (Schwartz, 1978; Desgranges et al., 1981).

**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'-deoxyuridine (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


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