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Gene Section
Review

PTMA (prothymosin, alpha)

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Identity

Other names: MGC104802; TMSA

HGNC (Hugo): PTMA

Location: 2q37.1

Note: Initially, the rat PTMA was isolated from fresh rat thymus, which contains the thymosin-alpha-1 sequence at its NH2 terminus (Haritos et al., 1984). A cDNA library from human spleen mRNA was constructed and screened for clones containing cDNAs coding for human PTMA (Goodall et al., 1986). A cDNA clones for human PTMA was also identified in cDNA libraries from staphylococcal endotoxin A-stimulated normal human lymphocytes (Eschenfeldt et al., 1986). Szabo et al. isolated a genomic clone encoding human PTMA with the 5'-regulatory region (Szabo et al., 1993). They used this 5'-flanking cloned probe, and then confirmed that human genomic PTMA gene was localized to chromosome 2.

DNA/RNA

Description

The human PTMA cDNA sequence has an open reading frame that was more than 90% identical to the rat PTMA gene, with significant homology extending into the 5' and 3' flanking regions (Frangou-Lazaridis et al., 1988).
NM_001099285.1, NP_001092755.1 prothymosin, alpha isoform 1; NM_002823.4, NP_002814.3 prothymosin, alpha isoform 2: Two named isoforms [FASTA] produced by alternative splicing.

Pseudogene

The six members of the human PTMA gene family have been cloned and sequenced. One gene (PTMA) was functional, and the remaining five genes are processed pseudogenes (Manrow et al., 1992).

Protein

Description

PTMA is a small, 12.4 kDa protein. It is a 109-111 amino acid long polypeptide as the precursor of thymosin alpha-1. The encoded human PTMA protein is a highly acidic (54 residues out of 111) and shared over 90% sequence homology with rat PTMA. The primary structure of PTMA is highly conserved and shows a number of important features. The first 28 amino acids of its sequence correspond to those of thymosin-alpha-1. It has a central acidic region (residues 41-85) comprising of glutamic and aspartic residues. Neither type of secondary structure has been detected. Thymosin-alpha-1 appeared at positions 2-29 of the PTMA.

Localisation

Subcellular location:
Nucleus: Normally, PTMA protein can be seen in nuclei of normal cells in various mammalian tissues (Haritos et al., 1984; Clinton et al., 1991; Palvimo et al., 1990; Manrow et al., 1991; Watts et al., 1989). PTMA is an abundant mammalian acid nuclear protein. Most intracellular PTMA protein appears in the nucleus, which may correlated with increased proliferation as measured by expression

of Ki67 nuclear antigen.
Cytoplasm: PTMA protein is also detected in the cytoplasm. PTMA transports between the nucleus and neighbouring cytoplasm. PTMA is a cytosol protein with functions such as anti-apoptosis (Jiang et al., 2003).

Function

Summary
PTMA has been shown to serve essential biological functions. However, its exact physiologic roles remain to be elucidated. In general, PTMA is associated with cellular proliferation and carcinogenesis (Eschenfeldt et al., 1986), cellular and viral transcription (Cotter et al., 2000), protection against apoptosis and chromatin remodelling (Karetsou et al., 1998).
PTMA may have a dual role both intracellulary and extracellulary.
The intracellular roles of PTMA are 1) cell proliferation / differentiation, 2) chromatin remodelling, 3) antiapoptotic activity through inhibition of apoptosome formation, and so on.
The extracellular roles of PTMA are 1) immunoenhancing activity by stimulating immune responses, and so forth.
Intracellularly, PTMA acts both in the nucleus (Manrow et al., 1991) and in the cytoplasm. Both nuclear and cytoplasmic PTMA play central roles in cellular functions due to its subcellular localization.
In the nucleus, PTMA affects the activity of several gene transcriptions. It plays an important role in transcription regulation. PTMA promote transcriptional activity of the estrogen receptor (ER) by sequestering a repressor of ER from the ER complex (Martini et al., 2000). PTMA binds to histone H1 known as a major regulator of chromatin structure (Díaz-Jullien et al., 1996) and cooperates in nucleosome assembly relating to chromatin remodelling (Gomez-Marquez et al., 1998). The effect of PTMA on chromatin remodelling is mediated, at least partially, through histone acetyltransferases.
In the cytoplasm, PTMA is involved in protection against apoptosis. It negatively regulates proapoptotic pathways (Jiang et al., 2003). PTMA has a significant antiapoptotic role in the cytoplasm by directly inhibiting the apoptosome, a complex in the execution of apoptosis. PTMA inhibits caspase 9 activation by blocking apoptosome formation.
Extracellularly, PTMA induces T cell maturation, differentiation and in vitro proliferation in response to soluble and cellular antigens (Baxevanis et al., 1990). PTMA demonstrated to present distinct immunoenhancing activity, stimulating immune responses in vitro and in vivo.
Cell proliferation / differentiation
Many previous reports clearly show that PTMA participates in developmental processes like cell proliferation and/or differentiation (Dosil et al., 1990). PTMA is required for cell division, growth, and survival (Piñeiro et al., 2000). It is also up-regulated in proliferating, transcriptionally active cells. PTMA gene level is elevated in normal proliferating tissue, but repressed in quiescent cells.
PTMA is correlated with increased proliferation as measured by expression of Ki67 nuclear antigen (Bianco et al., 2002) and proliferating cell nuclear antigen (PCNA) (Roson et al., 1993). PTMA is established as a proliferation marker.
Chromatin remodelling
PTMA interacts with histones and affects chromatin remodelling processes. PTMA binds to histone H1 known as a major regulator of chromatin structure (Díaz-Jullien et al., 1996) and cooperates in nucleosome assembly relating to chromatin remodelling (Gomez-Marquez et al., 1998). PTMA is involved in transcriptional regulation of histone acetylation. The effect of PTMA on chromatin remodelling is mediated, at least partially, through histone acetyltransferases.
Structurally, the interaction between PTMA and histones can be explained by the presence of its highly acidic domain (aspartate/glutamate between residues 41 and 85). The first 28 amino acids in the PTMA sequence can also bind core histones with high affinity in vitro.
Anti-apoptosis / Negative regulation of caspase activity
The antiapoptotic activity of PTMA occurs through inhibition of apoptosome formation. PTMA negatively regulated caspase-9 activation by inhibiting apoptosome formation (Jiang et al., 2003). Elimination of PTMA expression by RNA interference sensitized cells to ultraviolet irradiation-induced apoptosis.
Immunoregulatory role of PTMA
PTMA has been reported to exert in vitro immunomodulatory effects on autoimmune diseases. PTMA demonstrated to present distinct immunoenhancing activity, stimulating immune responses in vitro and in vivo.
PTMA induces T cell maturation, differentiation and in vitro proliferation in response to soluble and cellular antigens (Baxevanis et al., 1990). PTMA upregulates MHC class II gene expression in various cell types, including tumor cell lines (Baxevanis et al., 1992). PTMA may also mediate immune function by conferring resistance to certain opportunistic infections.
Radiation resistance
Recently, the association between PTMA expression and radiation resistance has been reported (Ojima et al., 2007). PTMA was significantly up-regulated in radioresistant human colon cancer cell lines. Among rectal cancer patients who treated with preoperative chemoradiotherapy, PTMA expression was significantly higher in non-responders who didn't histologically respond to chemoradiotharapy.
These lines of evidence indicate that PTMA may be a novel marker for predicting radiotherapy response.
Regulation

E2F (Vareli et al., 1996) and c-myc (Eilers et al., 1991) are important transcription factors that positively regulate the PTMA gene promoter.
E2F is one of the important transcription factors known to regulate cell cycle and cell proliferation (Vareli et al., 1996). E2F can activate the PTMA promoter and induces PTMA.
C-myc is one of significant proto-oncogenes implicating in normal proliferation and cell transformation. The transcriptional activation of c-myc leads to an increase in the level of transcription of PTMA. PTMA is a transcriptional target of c-myc. C-myc directly regulates the expression of PTMA gene by binding to the E-box of its promoter (Gaubatz et al., 1994). PTMA mRNA levels vary with c-myc expression during tissue proliferation, viral infection, and heat shock (Vareli et al., 1995). PTMA is considered as a downstream effector of the c-myc signalling pathway.
Oncogenic properties
PTMA has a capability of transforming rodent fibroblast cells like in a manner similar to Ras (Orre et al., 2001). PTMA is capable of inducing significant feature of transformed cells. Increased PTMA expression accelerates cellular proliferation. Because of its proliferative activity and overexpression in human cancers, PTMA may function as a cellular oncogene. Overexpression of c-myc, proto-oncogene stimulates cell cycle progression, cell proliferation, and induces cell transformation. Increased c-myc mRNA leads to an increase in PTMA mRNA. PTMA expression correlated with c-myc expression in human colon (Shiwa et al., 2003; Mori et al., 1993) and hepatocellular carcinoma (Wu et al., 1997). In addition, PTMA inhibits apoptosis by preventing formation of the apoptosose (Jiang et al., 2003). The observation that PTMA is a negative regulator of apoptosis indicates that it is a transforming oncoprotein and that its overexpression is associated with human cancers. Although PTMA does not have sequence homology to any other known oncogenes such as ras, it is considered as a growth-promoting and anti-apoptotic oncoprotein.

Homology

PTMA is highly conserved and broadly distributed in mammalian tissues.

Implicated in

Note
PTMA has been reported to present in various human malignancies. PTMA expression is higher in human cancer tissues than in adjacent normal tissues. Therefore, it may be considered as an oncoprotein or novel tumor marker. In several human cancers, PTMA expression has been related to cancer development, progression, and survival.

Breast cancer

Prognosis
PTMA expression is higher in breast cancer tissue than in normal breast tissue (Tsitsilonis et al., 1998). It correlates with proliferation status and metastatic potential of breast cancer (Dominguez et al., 1993; Magdalena et al., 2000). PTMA levels correlated with the number of positive axillary lymph nodes, risk of tumor recurrence and survival. PTMA is considered as a prognostic factor in breast cancer (Traub et al., 2006).

Bladder cancer

Note
Increased PTMA expression was found in human bladder cancers compared with the paired normal adjacent bladder tissue (Tsai et al., 2009).

Lung cancer

Prognosis
PTMA mRNA levels in lung cancer tissues were higher than those in normal lung tissues. PTMA overexpression in lung cancer was correlated with a poor prognosis (Sasaki et al., 2001a).

Gastric cancer

Note
PTMA is overexpressed in gastric adenocarcinoma (Wang et al., 2007; Leys et al., 2007).

Thyroid cancer

Note
PTMA mRNA levels were found significantly elevated in well-differentiated carcinomas in relation to adenomas and goitres, an event possibly linked to the proliferation activity of thyroid follicular cells (Letsas et al., 2007).

Neuroblastoma

Prognosis
PTMA mRNA levels were significantly correlated with proto-oncogene, N-myc, which is associated with more malignant behavior of neuroblastoma (Sasaki et al., 2001b).

Hepatocellular carcinoma

Note
PTMA mRNA levels were two- to 9.2-fold higher in tumoral tissues than in adjacent non-tumoral tissues in 14 of 17 patients with HCC (Wu et al., 1997). PTMA mRNA levels were significantly correlated with c-myc mRNA levels suggesting that such correlation is possibly involved in the tumorigenic process.

Prostate cancer

Note
PTMA expression is involved in the differentiation

and progression of human prostate cancers (Suzuki et al., 2006).

Colorectal cancers

Note

PTMA was overexpressed in human colorectal cancers compared with adjacent normal tissues. There was a significant correlation between the PTMA expression and c-myc expression (Shiwa et al., 2003; Mori et al., 1993).

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