TPD52 (tumor protein D52)

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Identity

Other names: D52, N8L, PC-1, PrLZ, hD52
HGNC (Hugo): TPD52
Location: 8q21.13
Local order: On the reverse strand.

DNA/RNA

Description

The TPD52 gene is found on chromosome 8, at location 81109658-81246391 bp. It is composed of at least 9 exons spanning a genomic region of 138.88 kb and the open reading frame of the coding region is 555 bp.

Transcription

Experimentally, an increase in TPD52 protein or mRNA transcript levels has been demonstrated or predicted following a number of different types of stimuli, such as hormone receptor activation (using dihydrotestosterone (DePrimo et al., 2002), estradiol (Byrne et al., 1996) and the synthetic androgens R1881 (DePrimo et al., 2002; Nelson et al., 2002; Rubin et al., 2004) and methyltrienolone (Wang et al., 2004)), immune receptor activation (toll-like receptor 4 (TLR-4) using bacterial Lipopolysaccharide (LPS) and triggering receptors expressed on myeloid cells 1 (TREM-1) using anti-TREM-1 cross-linking antibody (Dower et al., 2008), Erbb2 over-expression (Landis et al., 2005), Platelet-Derived Growth Factor (PDGF) signalling (Ma et al., 2005) and BRCA1 tumor suppressor (containing a single amino acid substitution specifically at Ser1841Asn) expression (Crugliano et al., 2007). A decrease in TPD52 transcript levels has been observed or predicted following treatment with the differentiating agent 12-O-tetradecanoylphorbol-13-acetate (TPA) (Byrne et al., 1996), myc oncoprotein overexpression (Guo et al., 2000) and MyoD gene knockdown (Asakura et al., 2007).

Pseudogene

No human pseudogene for TPD52 has been identified (see Pseudogene In Family).

Protein

Description

The TPD52 gene encodes multiple proteins, predominantly TPD52 (184 aa, isoform 3, accession no. NP_005070.1) and PrLZ/PC-1 (224 aa, isoform 1, accession no. NP_001020423.1). Both are encoded by 6 exons, with the first exon being unique to each isoform. They share a coiled-coil motif located towards the N-terminus but possess alternate N-terminal domains. Since TPD52 is more ubiquitously expressed than PrLZ (for TPD52 expression, see Byrne et al., 1995 and Chen et al., 1996; for PrLZ expression, see Wang et al., 2004), TPD52 will be the primary focus of this summary.

TPD52 is a 184-amino acid polypeptide with a predicted molecular mass of 19.8 kDa. The protein is indicated to be largely hydrophilic, has a calculated isoelectric point of 4.75, and contains an identified phosphorylation site at Serine 136 (Chew et al., 2008; Thomas et al., 2010). Using glutaraldehyde cross-linking, Chen et al. (1997) showed that TPD52 is able to bind itself (also shown by Byrne et al., 1998; Sathasivam et al., 2001, and Thomas et al., 2001). Byrne et al. (1998) also showed that TPD52 binds the related TPD52L1 and TPD52L2 proteins. These authors proposed that TPD52 may exert and/or regulate its activities through interaction with itself and its related proteins and that the coiled-coil motif predicted within the TPD52 protein is necessary...
for interactions (Byrne et al., 1998). A subsequent analysis indicated that C-terminal regions may also facilitate and/or stabilise these interactions (Sathasivam et al., 2001).

The first heterologous binding partner identified for TPD52 was the proteolipid MAL2 (Wilson et al., 2001), which is similar to MAL, an integral component of the apical transport machinery in polarised cell types (Martin-Belmonte et al., 1998; Puertollano et al., 1999; Cheong et al., 1999). MAL2 was shown to be a binding partner for TPD52 using the yeast two-hybrid system (Wilson et al., 2001) and more recently to co-immunoprecipitate with TPD52 using Myc-MAL2 overexpressing MCF-10A breast cancer cells (Fanayan et al., 2009).

TPD52 also binds Annexin VI, which is involved in membrane trafficking, and this binding is Ca\(^{2+}\)-dependent (Thomas et al., 2002; Tiacci et al., 2005). TPD52 (along with Tip47, Rab5, Rab6 and Rab9) co-immunoprecipitated with the bacterial product ExoS, as shown by a study which examined the transport of ExoS from plasma membrane to perinuclear regions (Zhang et al., 2007a).

**Expression**

Early studies using Northern blot analysis undertaken by Byrne et al. (1995) showed strong expression of TPD52 transcripts in colon and kidney tissues. Chen et al. (1996) used the same technique to identify comparatively high TPD52 transcript levels in kidney, prostate, small intestine and kidney, as well as moderate levels in brain, liver, placenta, pancreas epithelia, and low levels in heart, lung, ovary, peripheral blood leukocyte, skeletal muscle, spleen, testis, and thymus tissues. Chen et al. (1997) followed up with immunohistochemistry and multiple tissue western blot analysis indicating strong detection of TPD52 protein in colon and kidney, moderate levels in brain and liver tissue, and low levels in heart, lung and skeletal muscle. Groblewski et al. (1999) used western blotting and immunofluorescence studies to identify high levels of TPD52 protein in colon epithelia and small intestine epithelia, as well as moderate expression in the lacrimal gland, pancreas, parotid gland, stomach epithelia and submandibular gland. More recently, Wang et al. (2004) identified high levels of the PrLZ transcript in prostate using a multiple tissue expression array, whilst Tiacci et al. (2005) found high levels of TPD52 protein via immunofluorescence in B cells (including plasma cells) and colon tissue, and moderate levels in stomach and pancreas epithelia.

**Localisation**

TPD52 is partitioned between soluble and insoluble cellular protein fractions (Groblewski et al., 1999; Balleine et al., 2000), suggesting that TPD52 may have multiple subcellular locations. TPD52 is abundant around secretory granules in the apical cytoplasm of epithelial cells of exocrine glands, gastrointestinal tissues and in cultured mucosal T84 cells of the rat (Groblewski et al., 1999; Kaspar et al., 2003a). Kaspar et al. (2003a) also showed that TPD52 exists in perinuclear regions of T84 cells, whilst Thomas et al. (2004) showed that TPD52 exists within or around both endocytic and exocytic compartments within rat pancreatic acinar cells. Using breast cancer samples, immunohistochemical analysis by Balleine et al. (2000) revealed TPD52 staining within the cytoplasm and less frequently in the perinucleus, whilst benign epithelial elements displayed little or no staining. Myeloma cells also strongly expressed TPD52 in the cytoplasm (Tiacci et al., 2005).

**Function**

At a subcellular level, TPD52 appears to be involved in plasma membrane-based exocytic (Thomas et al., 2001; Kaspar et al., 2003a; Kaspar et al., 2003b; Chew et al., 2008) and endocytic functions (Thomas et al., 2004), and trafficking within the exo- and endocytic pathways (Thomas et al., 2002; Thomas et al., 2004). At a cellular level, TPD52 has been shown to promote proliferation (Lewis et al., 2007; Zhang et al., 2007b; Shehata et al., 2008a; Li et al., 2009) and tissue invasion (Lewis et al., 2007), as well as B-cell maturation (Tiacci et al., 2005). However, a clear link between TPD52's subcellular and cellular influences has yet to be established.

TPD52 was initially predicted to function as a calcium-sensitive signalling molecule, since rabbit TPD52 is phosphorylated in gastric parietal cells upon cholinergic stimulation (Parente et al., 1996). At least two phosphorylation events for human and rat TPD52 have been demonstrated (Groblewski et al., 1996; Kaspar et al., 2003a; 2003b) and more are predicted (Olsen et al., 2006; Molina et al., 2007). Using mass spectrometry and site-directed mutagenesis, Chew et al. (2008) showed that the calcium/calmodulin-dependent phosphorylation of TPD52 on serine residue 136 may be mediated by CAMK2delta. Significantly, the time-course of such phosphorylation was found to correlate with exocytosis, suggesting that TPD52 may promote exocytosis following phosphorylation. Thomas et al. (2010) recently showed that this phosphorylation of TPD52 caused an increase of LAMP-1 exocytosis from CHO-K1 cells. This had earlier been suggested in studies involving stimulation of pancreatic (using cholecystokinin-octapeptide) and colonic (using carbachol) secretion in rat acinar and mucosal T-84 cells, respectively (Kaspar et al., 2003a; 2003b). On par with this, amylase was shown to be released from rat pancreatic acinar cells in a calcium-dependent manner, following the introduction of recombinant TPD52 (Thomas et al., 2001). Furthermore, TGF-beta1 was found to be secreted from stably transfected mouse Tpd52-expressing 3T3 fibroblasts (Lewis et al., 2007). However, it has not been determined if TPD52 is directly involved with the above-mentioned release of
TGF-beta1 or if this is perhaps a downstream consequence of TPD52 expression. TPD52 binds Annexin VI (Thomas et al., 2002; Tiacci et al., 2005) and MAL2 (Wilson et al., 2001) which have been implicated in clathrin-mediated endocytosis (Kamal et al., 1998; Thomas et al., 2002) and indirect apical transcytosis (de Marco et al., 2002), respectively. Using CCK-8 treatment in pancreatic acinar cells, Thomas et al. (2004) showed TPD52 to localise to early endosomes and the limiting membrane of zymogen granules, suggesting that TPD52 may play a role in protein and phospholipid distribution within the secretory pathway. They also recently examined LAMP-1 trafficking and AP-3/TPD52 co-localisation in CHO-K1 cells which suggested TPD52 may participate in lysosome-like vesicle formation (post-golgi) as well as endocytic retrieval (Thomas et al., 2010). TPD52's potential endocytic involvement was also demonstrated through its co-immunoprecipitation with the bacterial product ExoS (along with Tip47, Rab5, Rab6 and Rab9), perhaps enabling the transport of the bacterial product ExoS from endosome to golgi and perinuclear regions (Zhang et al., 2007a). TPD52 also binds family member TPD52L1, which itself has been implicated in the regulation of SNARE complexes on early endosomes (Proux-Gillardeaux et al., 2003).

Exogenous expression of TPD52 isoforms in various cell lines has produced increases in anchorage-independent colony formation (Lewis et al., 2007; Zhang et al., 2007b; Shehata et al., 2008a), proliferation (Lewis et al., 2007; Zhang et al., 2007b; Shehata et al., 2008a; Li et al., 2009), metastatic ability post-inoculation (Lewis et al., 2007), tumor volume post-inoculation (Zhang et al., 2007b; Li et al., 2009) and migration/invasion rate (Li et al., 2009). Also, a decrease in TPD52 level following siRNA treatment caused an increase in apoptosis in the SK-BR-3 breast cancer cell line (Shehata et al., 2008a). Zhang et al. (2007b) showed that stable transfection of TPD52 in LNCaP and its derivative androgen-independent C4-2 prostate cancer cell lines results in the phosphorylation of signalling intermediates that are also implicated in producing the above-mentioned phenotypes, namely AKT, Raf and GSK-3beta. The increased phosphorylation of AKT has since been confirmed by Ummani et al. (2008), who also examined the LNCaP cell line.

Homology

Subsequent to the characterisation of TPD52 in 1995 (Byrne et al., 1995), there have been three related genes described. These are TPD52L1 (D53) (Byrne et al., 1996), TPD52L2 (D54) (Nourse et al., 1998) and NYD-SP25/TPD52L3 (D55) (Cao et al., 2006). TPD52-like genes share about 50% nucleotide sequence homology, and are not similar to proteins of known function in any species (Nourse et al., 1998). TPD52 and TPD52-like genes appear to have evolved from ancestral TPD52-like sequences such as those found in Drosophila melanogaster and Caenorhabditis elegans through gene duplication events (Boutros et al., 2004).

Implicated in Various cancers

Note

Association to diseases (breast neoplasms; carcinoma, basal cell; neoplasms; ovarian neoplasms; prostatic neoplasms) and proposed to participate in processes (anatomical structure morphogenesis, B cell differentiation, secretion).

Disease

In situ hybridisation and Northern blot studies first revealed TPD52 overexpression in breast cancer (Byrne et al., 1995). Chen et al. (1996, 1997) also found TPD52 mRNA/protein to be expressed in breast cancer derived cell lines, as well as those derived from lung cancer, colon cancer, pancreatic cancer, prostate cancer, kidney cancer, leukemia and Burkitt's lymphoma. Other more recent investigations have confirmed TPD52 or PrLZ RNA/protein overexpression in prostate cancer (Rubin et al., 2004; Wang et al., 2004).

TPD52 overexpression has also been predicted via expression microarray studies for prostate (Rhodes et al., 2002; Ahram et al., 2002; Best et al., 2003), ovarian (Shridhar et al., 2001), endometrial (Risinger et al., 2003; Cai et al., 2007), hepatocellular (Chen et al., 2002), lung (Garber et al., 2001; Bhattacharjee et al., 2001), melanoma (Bittner et al., 2000; Zhou et al., 2004; Hoek, 2007; Roesch et al., 2007) and testicular germ cell tumours (Sperger et al., 2003; Skotheim et al., 2005; Korkola et al., 2006; Skotheim et al., 2006; McIntyre et al., 2007; Korkola et al., 2008). TPD52 protein overexpression has been confirmed in melanoma (Roesch et al., 2007) and testicular germ cell tumours (Alagaratnam et al., 2009).

Prognosis

Expression microarray studies have revealed TPD52 gene overexpression to be associated with adverse outcome for patients with breast cancer (Adler et al., 2006; Liu et al., 2007), prostate cancer (Bismar et al., 2006) and mantle cell lymphoma (Ma et al., 2007). Higher levels of TPD52 expression amongst breast cancer patients has also been shown to be associated with reduced overall patient survival (Shehata et al., 2008a).

Cytogenetics

Using TPD52 expression and relative TPD52 copy number studies in breast specimens, Balleine et al. (2000) first proposed TPD52 as a target gene driving increased copy number of 8q21. Similar studies have since identified an association between TPD52 copy number gain and TPD52 expression in prostate cancer (Rubin et al., 2004; Wang et al., 2004) and ovarian...
cancer (Byrne et al., 2005). TPD52 has also been found to be amplified and overexpressed in multiple myeloma (Largo et al., 2006), pancreatic cancer xenografts (Loukopoulos et al., 2007) and testicular germ cell tumours (Skothelm et al., 2006; McIntyre et al., 2007; Korkola et al., 2008). However, TPD52 overexpression may also occur in the absence of gene amplification or gain (Balleine et al., 2000; Adelaide et al., 2007).

Oncogenesis

An increase in TPD52 expression has been found to be a comparatively early event in breast (Porter et al., 2000). An increase in TPD52 expression has been found to be a comparatively early event in breast (Porter et al., 2000; McIntyre et al., 2007; Korkola et al., 2008). However, TPD52 overexpression may also occur in the absence of gene amplification or gain (Balleine et al., 2000; Adelaide et al., 2007).

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