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Gene Section
Review

TPX2 (TPX2, microtubule-associated, homolog (Xenopus laevis))

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Identity

Other names: C20orf1, C20orf2, DIL-2, DIL2, FLS353, GD:C20orf1, HCA519, HCTP4, REPP86, p100
HGNC (Hugo): TPX2
Location: 20q11.21

DNA/RNA

Description

The TPX2 locus is on the q arm of chromosome 20; position 30326904 to 30389603, forward strand (NCBI, 22974).

Transcription

The 3685 bp mRNA (NCBI Reference Sequence: NM_012112.4) contains 18 exons (16 coding); the processed cDNA is of 2244 bp. Ensembl reports the existence of a second transcript, containing 1 additional exon (ENST00000340513). TPX2 is expressed in proliferating cells; the TPX2 transcript was detected at high levels in human placenta, thymus and testis, while it was barely detectable in brain, heart, lung and pancreas (Manda et al., 1999; Wang et al., 2002; Satow et al., 2010).

Pseudogene

No pseudogenes described in humans.

Protein

Description

747 aa; MW: 85653 Da.
Human TPX2 was initially identified as a nuclear protein of apparent molecular weight of 100 kDa expressed in proliferating cells, and named p100 (Heidebrecht et al., 1997); it was subsequently re-isolated in the search for mitotic targets of RanGTP as the homolog of X. laevis TPX2 (Gruss et al., 2001).
Human TPX2 harbours distinct functional domains:
- TPX2 is a microtubule-associated protein; both the full length protein and the N-terminus (amino acids 1-352) are able to bind microtubules in vitro (Schatz et al., 2003; Trieselmann et al., 2003). Additional regions in the C-terminus of TPX2 are involved in direct or indirect binding to microtubules in cells (Trieselmann et al., 2003). Domain characterisation of the Xenopus homolog also indicates the presence of one or more microtubule-binding domains in the N-terminus of TPX2; the C-terminal region has no direct affinity for microtubules but is required for localisation to spindle poles (Brunet et al., 2004).
- A non canonical nuclear localisation signal (NLS) centered around amino acids 314-315 (Schatz et al., 2003) mediates binding of TPX2 to importin alpha. Structural work has confirmed the association of the corresponding residues 284-287 in the Xenopus homolog protein to the "minor" NLS-binding site of importin alpha and has shown a second region (residues 327-330 of Xenopus TPX2) contacting the "major" NLS-binding site (Giesecke and Stewart, 2010).

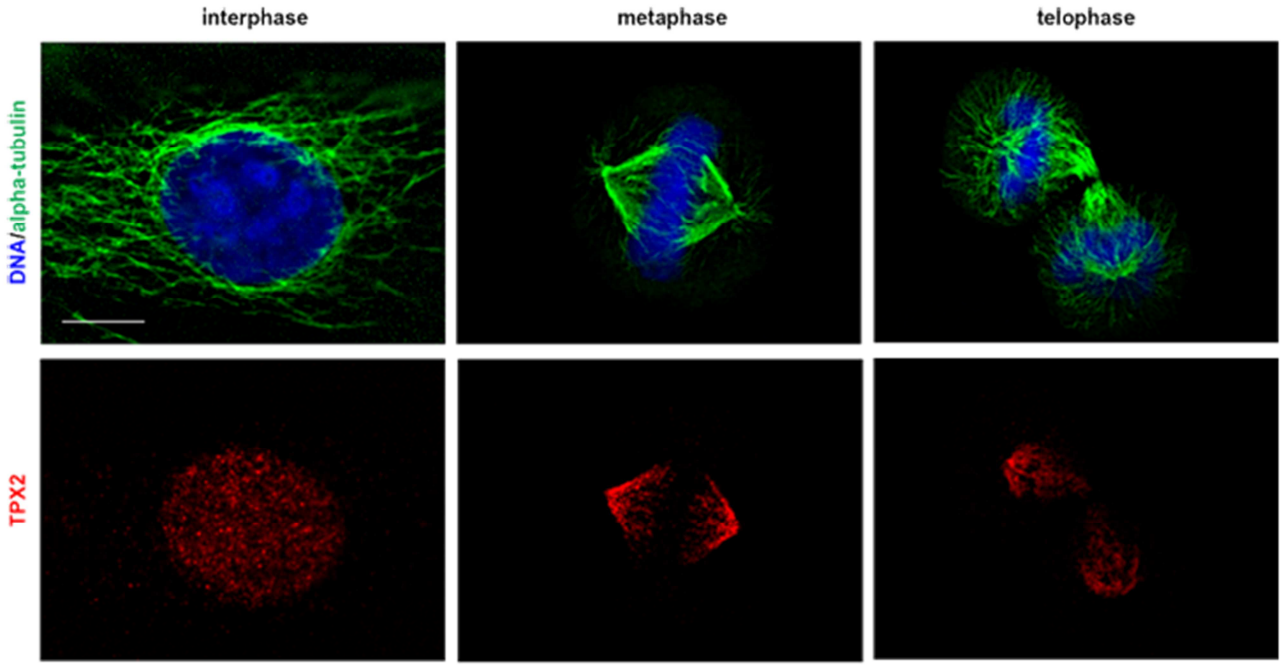

Figure 1. TPX2 localisation in human cells. Immunofluorescence images of U2OS osteosarcoma cells stained with DAPI (blue), anti-alpha-tubulin (green) and anti-TPX2 (red) antibodies show the nuclear localisation of TPX2 in interphase and TPX2 association to spindle microtubules in different mitotic stages. Scale bar: 10 µm.

- A KEN box (87-89) degradation motif is required for recognition by APC/C^{Cdh1} (Stewart and Fang, 2005).
- The N-terminal region (residues 1-43; Bayliss et al., 2003) is required for the interaction with, and activation of, the Aurora-A kinase.
- An evolutionary conserved region of 35 amino acids at the C-terminus has been shown both in Xenopus and mouse TPX2 to bind the Eg5 kinesin (Eckerdt et al., 2008; Ma et al., 2010).

Expression

TPX2 is expressed in a cell cycle-regulated manner; it appears in S phase and protein levels remain high in G2 and mitosis, until telophase when TPX2 is down-regulated via APC/C^{Cdh1}-dependent degradation (Heidebrecth et al., 1997; Gruss et al., 2001; Stewart and Fang, 2005). TPX2 is differentially expressed in tumor vs non-transformed cells (see below).

Localisation

TPX2 localises to nuclei of interphase cells (S and G2); after nuclear envelope breakdown it associates with spindle microtubules; in late anaphase and telophase it also localises to the spindle mid-zone (Heidebrecht et al., 1997; Gruss et al., 2002; Garrett et al., 2002; figure 1).

Function

Spindle assembly: TPX2 is a RanGTP-regulated spindle assembly factor (Gruss et al., 2001). An important contribution to the understanding of the mechanisms through which TPX2 acts in spindle assembly has been provided by studies that made use of the Xenopus egg extract system (Gruss and Vernos, 2004 and references therein).

Evidence obtained in mammalian cells support the notion that TPX2 plays a key role in spindle formation and function. Mitotic functions of TPX2 are negatively regulated by the binding to importin alpha and beta; the presence of RanGTP, by dissociating the complex between TPX2 and import receptors, induces the release of active TPX2 (Gruss et al., 2001). Indeed, excess TPX2 is able to rescue spindle pole organisation defects induced by importin beta overexpression in human cells (Ciciarello et al., 2004), pointing out the functional antagonism between TPX2 and import receptors in spindle assembly.

TPX2 acts in spindle organisation by:

i) its direct ability to induce microtubule assemblies and to bundle microtubules (Schatz et al., 2003);

ii) its targeting function: TPX2 recruits several mitotic regulators to the spindle, i.e. the Aurora-A kinase (Kufer et al., 2002), the kinesins hklp2 (Vanneste et al., 2009; Tanenbaum et al., 2009) and Eg5 (Ma et al., 2011b) and the scaffold attachment factor A (SAF-A; Ma et al., 2011a);

iii) regulation of specific mitotic factors: TPX2 interacts with the Aurora-A kinase and activates it, by stabilising it in the active conformation (Bayliss et al., 2003); in addition, TPX2 modulates Aurora-A protein stability, by counteracting proteasome-dependent Aurora-A degradation (Giubettini et al., 2011). TPX2 also regulates the activity of the Eg5 kinesin: in vitro

assays show that TPX2 reduces the rate of Eg5-dependent microtubule gliding and microtubule-microtubule sliding (Ma et al., 2011).
Consistently, its inactivation in cultured mammalian cells impairs microtubule nucleation from chromosomes, and to a lesser extent from centrosomes, as well as organisation of microtubules within the spindle and cohesion of spindle poles (Garrett et al., 2002; Gruss et al., 2002; De Luca et al., 2006; Tulu et al., 2006; Bird and Hyman, 2008).
Neurogenesis in vertebrate brain: Neural progenitor cells in the apical-most region of the neuroepithelium, or ventricular zone, exhibit interkinetic nuclear migration (INM): their nuclei migrate apically in synchrony with cell cycle progression, so that mitosis occurs at the apical surface of the ventricular zone. TPX2 has been recently reported to promote interkinetic nuclear migration in mouse neural cells, by re-organising apical microtubules during the G2 phase (Kosodo et al., 2011).
DNA damage response (DDR): recent data show that TPX2 is involved in DDR to ionising radiations, by modulating the levels of γ-H2AX; TPX2 localises to DNA double strand breaks and interacts with DDR factors such as MDC1 (Neumayer et al., 2012).
Previous data suggested a link between TPX2 and DDR: i) TPX2 is a putative substrate of the ATM/ATR kinases, as revealed in a large-scale proteomic screening (Matsuoka et al., 2007); ii) a functional interplay has been shown between Xenopus TPX2, the Aurora-A kinase and the p53 oncosuppressor (Pascreau et al., 2009).

Homology

TPX2 orthologs have been identified in all classes of vertebrates, with Xenopus, mouse and human TPX2 being the best characterised.
TPX2-like proteins have been described in plants (Vos et al., 2008; Evrard et al., 2009), C. elegans (Ozlü et al., 2005) and Drosophila melanogaster (Goshima, 2011).

Implicated in

Various cancers

Oncogenesis
The TPX2 gene is located on the long arm of chromosome 20, in a region that is frequently amplified in cancer. Growing evidence, described in detail in sections below, indicate that TPX2 levels are increased in tumors and suggest that TPX2 is involved in tumorigenesis. An overall evaluation of TPX2 overexpression in different cancer types can be obtained with the Oncomine database (www.oncomine.org), which collects data from several microarrays; a recent study using Oncomine shows that TPX2 is significantly overexpressed in about 25% of analyses of tumor vs normal tissues and that it ranks among the first 10% overexpressed genes in the vast majority of cases (Asteriti et al., 2010).
Association of increased TPX2 levels, chromosomal instability (CIN) and cancer has also been highlighted: TPX2 ranked first in a CIN25 signature, the overexpression of which is predictive of poor clinical outcome (Carter et al., 2006). A TPX2 gene signature has also been recently identified as associated with metastatic progression in breast cancer (Hu et al., 2012).

Brain cancer

Prognosis
Analysis of astrocytoma tissue samples showed positive TPX2 staining, while TPX2 was not detected in normal brain tissues; in addition, TPX2 expression levels were higher in high-grade, compared with low-grade, astrocytomas.
The median survival of patients correlated with TPX2 levels, with high TPX2 being associated with overall poor survival (Li et al., 2010).
TPX2 was also identified among 9 genes which are significantly overexpressed in grade III vs grade I meningiomas (Stuart et al., 2011) and among 14 genes with elevated expression in high-risk neuroblastomas with 1p loss and MYCN amplification (Ooi et al., 2012).

Oral squamous cell carcinoma

Prognosis
Expression levels of TPX2 were not related with tumor size, lymph node invasion or histopathologic grading (Fenner et al., 2005).
Oncogenesis
TPX2 expression levels, analysed by RT-PCR (Shigeishi et al., 2009a) or immunohistochemistry (Fenner et al., 2005), were significantly higher compared with normal oral tissues.

Salivary gland carcinoma

Oncogenesis
Levels of TPX2 mRNA were analysed by RT-PCR in 20 human salivary gland carcinomas compared with 6 normal submandibular glands and resulted higher in all tumor samples (Shigeishi et al., 2009b).

Lung cancer

Note
Human bronchial epithelial cells malignantly transformed by anti-BPDE (16HBE-C) displayed abnormal levels of phosphorylated TPX2 on tyrosine residues (Zhang et al., 2008).
Prognosis
Three studies indicate the prognostic value of TPX2 overexpression in adenocarcinomas (Kadara et al., 2009; Li et al., 2013) and squamous cell carcinoma (Ma et al., 2006): TPX2 expression is associated with tumor grade and stage and poor survival rates. In particular, TPX2 is among the top genes in prognostic

signatures identified as classifiers for overall survival of patients (Kadara et al., 2009; Li et al. 2013).

Oncogenesis

Several studies report increased TPX2 expression levels in primary lung tumors (adenocarcinomas, squamous cell carcinoma, small cell carcinoma) and lung cancer cell lines, compared to controls (Manda et al., 1999; Tonon et al., 2005; Ma et al., 2006; Zhang et al., 2008; Kadara et al., 2009; Li et al., 2013).

Colon cancer

Oncogenesis

TPX2 overexpression in colorectal cancer was observed by suppression subtractive hybridisation (SSH) method applied to a primary stage III rectal adenocarcinoma and the matched non-neoplastic mucosa (Hufton et al., 1999).

In addition, protein levels of TPX2 and of its partner Aurora-A correlate significantly with chromosome 20q DNA copy number status: TPX2 and Aurora-A are therefore implicated in the 20q amplicon-driven progression of colorectal adenoma to carcinoma (Sillars-Hardebol et al., 2012).

Liver cancer

Oncogenesis

The TPX2 transcript is expressed at high levels in hepatocellular carcinomas, compared with weak expression in paired normal tissues (Wang et al., 2002; Satow et al., 2010).

Pancreatic cancer

Prognosis

Increased expression of TPX2 was associated with poor survival and significantly correlated with histological grade in two independent cohorts (from Germany and Maryland; Zhang et al., 2012).

When cohorts were combined, and stratified by resection margin status (positive vs negative), TPX2 was associated with cancer-specific mortality in resection margin-positive patients and with prognosis in resection margin-negative patients.

Oncogenesis

Low copy-number amplification of TPX2, associated with increased mRNA and protein levels, was observed in pancreatic cancer cell lines (Warner et al., 2009); the TPX2 gene is also included in an amplicon identified by microarray analysis of pancreatic ductal adenocarcinoma (Tonon et al., 2005). Immunohistochemical staining of tissue microarrays showed increased TPX2 levels in pancreatic tumors compared with the normal counterparts (Warner et al., 2009; Zhang et al., 2012).

Ovarian cancer

Note

The Aurora-A kinase, which interacts with, and is regulated by, TPX2 is also differentially expressed in ovarian carcinomas vs adenomas (Scharer et al., 2008).

Prognosis

A comparative analysis revealed a stronger (15 to 27 fold) overexpression of TPX2 in primary ovarian carcinomas compared with non-malignant adenomas (Scharer et al., 2008).

Oncogenesis

A high resolution genome wide copy number analysis combined with matching expression data from primary epithelial ovarian carcinomas of various histotypes showed that TPX2 is among the most significantly differentially expressed genes in a chromosome 20 region frequently amplified in ovarian cancer (Ramakrishna et al., 2010).

Cervical cancer

Prognosis

TPX2 expression levels in cervical squamous cell carcinoma positively correlate with tumor stage and grade, and lymph node metastasis (Chang et al., 2012).

Oncogenesis

Copy number increase of chromosome 20q, where the TPX2 gene is located, is frequently observed in cervical cancers; indeed TPX2 is reported among the 26 genes that are significantly overexpressed as consequence of 20q gain (Scotto et al., 2008). TPX2 mRNA and protein are highly expressed in cervical cancer, while its expression is almost absent in normal cervical tissues (Chang et al., 2012).

Bladder cancer

Oncogenesis

RNA microarrays and RT-PCR analyses showed significant upregulation of TPX2 in urothelial carcinomas of the bladder compared with normal urothelium (Zhou et al., 2013).

Mesothelial tumors

Prognosis

Immunostaining of malignant mesothelioma samples compared to benign reactive mesothelial hyperplasia showed significant overexpression of TPX2 in malignant samples, suggesting that TPX2 represents a useful marker in this respect (Taheri et al., 2008).

To be noted

Note

Growing evidence highlights the therapeutic potential of TPX2 inactivation. Two RNAi-based screenings identified TPX2 among essential genes for tumor survival and hence the most promising target candidates for anti-cancer strategies (Morgan-Lappe et al., 2007; Martens-de Kemp et al., 2013). Several studies provide direct demonstration of the anti-proliferative effects of TPX2 inactivation in cancer cells of different tumor types (Morgan-Lappe et al., 2007; Zhang et al., 2008; Warner et al., 2009; Li et al., 2010; Satow et al., 2010; Chang et al., 2012; Vainio et

al., 2012; Martens-de Kemp et al., 2013). In addition, TPX2
inactivation significantly reduced tumor growth in xenografts models based on inoculation in nude mice of pancreatic or hepatocellular carcinoma cells (Warner et al., 2009; Satow et al., 2010).

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