TACC3 (transforming, acidic coiled-coil containing protein 3)

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Identity

Other names: ERIC1; MGC117382; MGC133242
HGNC (Hugo): TACC3
Location: 4p16.3

DNA/RNA

Description
The gene is composed of 16 verified exons spanning 23.6 kb.

Transcription
Encodes a single confirmed 2788 nt transcript (NM_006342) (Still et al., 1999), although one additional transcript with two additional small 5’ coding exons between exon 1 and the first coding exon (exon 2), based on NM_006342, is indicated based on several cDNAs that may however be from suspect cDNA libraries (see UCSC Genome Bioinformatics Site (http://genome.ucsc.edu)). Four additional transcripts variants are suggested based on singleton Expressed sequence tags in tumor cell lines (AW516785, BE552327, BX331864) and/or stem cell progenitors (AV761182, CX872433).

Pseudogene
None.
**Protein**

**Description**
TACC3 encodes a single protein of 838 amino acids with a molecular mass of 90 kDa (Still et al., 1999). The protein is heavily phosphorylated based on direct evidence and based on predictions from the Xenopus and mouse orthologs (Beausoleil et al., 2004; Beausoleil et al., 2008; Kinoshita et al., 2005; Yu et al., 2007; Cantin et al., 2008; Dephoure et al., 2008). Thus, human TACC3 migrates at approximately 150 kDa in SDS-PAGE. Additional variants are suggested based on singleton cDNAs (see above) but their predicted protein isoforms have not been confirmed.

**Expression**
High levels during early (mouse) embryogenesis, in particular during early differentiation of specific tissues (Sadek et al., 2003). In adult tissues, expression is relatively limited, with high levels noted in hematological tissues such as the thymus, spleen and leukocytes, and reproductive tissues, especially meiotic cells of the testes and ovary (Still et al., 1999; Sadek et al., 2003).
Epithelial layers of the lung, mammary gland and ovary express TACC3 and alterations in expression are noted during tumorigenesis (see below). Expression in human adult tissues is summarized in Lauffart et al. 2006.

**Localisation**

Human (and mouse) TACC3 is located in the interphase nucleus and/or cytosol, depending on cell type and cancer type (Gergely et al., 2000; Aitola et al., 2003; Lauffart et al., 2005; Jung et al., 2006; Vetteaikkorumakankauv et al., 2008). TACC3 does not however contain a classical nuclear localisation signal (Still et al., 1999). TACC3 associates with the centrosome in a cell cycle dependent manner (Gergely et al., 2000). Phosphorylation of TACC3 by Aurora A on key serine residues is required for this interaction (Kinoshita et al., 2005; LeRoy et al., 2007). Overexpression of TACC3 from artificial constructs can result in accumulation in the cytosol of some cells resulting in oligomerisation in punctate structures (Gergely et al., 2000).

**Function**

Gene knockout and knockdown studies in mouse have indicated that TACC3 is vital for embryonic development. A functionally null TACC3 mutant dies during mid to late gestation due to excessive apoptosis affecting hematopoietic and other organ systems (Piekorz et al., 2002). Hypomorphic alleles result in defects in mitosis affecting mesenchymal sclerotome and therefore the axial skeleton (Yao et al., 2007). These mutational mouse models indicate that TACC3 has a role in chromosomal alignment, separation and cytokinesis and that TACC3 can be associated with p53-mediated apoptosis.

TACC3 has a well characterized function in microtubule dynamics, particularly during mitosis, based on mutational analysis (see above) and physical interactions with Aurora A and Aurora B kinases, CKAP5 (ch-TG/XMAP215) and AKAP9 via the TACC domain (see Peset and Vernos, 2008 for review). Interaction with CEP120 is important in interkinetic nuclear migration and maintenance of neural progenitor self-renewal during the development of the neocortex (Xie et al., 2007). Phosphorylation of Ser34, Ser552 and Ser558 by Aurora A are required for localization to centro-somes and is necessary for recruitment of CKAP5 and nucleation of microtubules (Kinoshita et al., 2005; LeRoy et al., 2007). Ser25, Thr59, Ser71, Ser317, and Ser 434 are presumed targets for cyclin dependent kinases in mitotic HeLa cells (Yu et al., 2007; Cantin et al., 2008; Dephoure et al., 2008). By homology, Ser558 phosphorylation by TPX2 is required for nucleation of microtubules in meiotic oocytes (Brunet et al., 2008). TACC3 also has a defined role in interphase cells as a transcriptional cofactor for the ayrl-nuclear translocator protein (Sadek, 2000), FOG1 (Garriga-Canut and Orkin, 2004; Simpson et al., 2004) and is a possible indirect activator of CREB via FHL family of coactivator/corepressor proteins (Lauffart et al., 2007b). Roles in transcriptional regulation have also been proposed based on TACC3 binding to GAS41 (YEATS4) via the SDP repeat, histone acetyl transferases hGCN5L2 (KAT2A), pCAF (KAT2B), and retinoid X-receptor beta via the TACC domain (Gangisetty, 2004; Lauffart et al., 2002; Vetteaikkorumakankauv et al., 2008). TACC3 functionally interacts with MBD2 bound to methylated promoters, promoting transcription by displacement of HDAC2 and recruitment of KAT2B (Angrisano et al., 2006). Human TACC3 may be involved in transcriptional termination and/or pre-mRNA splicing through TTF2 (Leonard et al., 2003). TACC3 can interact with BARD1, BRCA1 and p53 and has been shown to have some protective affects against adriamycin-mediated DNA damage in ovarian cancer cells (Lauffart et al., 2007a). Phosphorylation of the last amino acid of the SDP repeat, Ser434, is noted in nuclear extracts of HeLa (Beausoleil, 2004; Beausoleil, 2006), although its functional significance is unknown.

**Homology**

Member of the TACC family, based on the presence of the evolutionarily conserved approximately 200 amino acid carboxy terminal coiled coil domain (TACC domain) (Still et al., 1999; Still et al., 2004). TACC3 orthologues are noted in all vertebrates sequenced to date (Still et al., 2004 and Still unpublished). However, the central region between the conserved N-terminal region and the TACC domain is highly variable in size and sequence. The SDP repeats are noted within the central region in most vertebrates except mouse and rat (Still et al., 2004).

**Mutations**

**Note**

Somatic mutations noted in ovarian cancer samples (Lauffart et al., 2005; Eslinger, 2006).
**Implicated in**

**Ovarian cancer**

**Prognosis**
Overexpression of TACC3 is associated with chemoresistance in ovarian tumors (L'Esperance et al., 2006).

**Oncogenesis**
Total cellular expression or nuclear localization lost in ovarian cancer (Lauffart et al., 2005).

**Non-small cell lung cancer**

**Prognosis**
High TACC3 expression is an independent prognostic indicator associated with significantly shorter median survival time. TACC3 expression was correlated with p53 expression and poor prognosis (Jung et al., 2006).

**Oncogenesis**
A high level of TACC3 expression was observed in 14.8% of cases of non small cell lung cancer, predominantly of the squamous cell carcinoma type (Jung et al., 2006).

**Breast cancer**

**Prognosis**
Loss of TACC3 is observed as a predictor of poor prognosis in breast cancer (Conte et al., 2002).

**Oncogenesis**
TACC3 protein downregulated in breast cancer (Conte et al., 2002).

**Multiple myeloma**

**Prognosis**
TACC3 overexpression correlates with the t(4;14) translocation that is associated with poor prognosis (Stewart et al., 2004).

**Oncogenesis**
TACC3 is located close to the MMSET gene that is rearranged in t(4;14) translocation (Still et al., 1999). This rearrangement upregulates the TACC3 gene (Stewart et al., 2004).

**Thyroid cancer**

**Prognosis**
Reduction of expression associated with increased malignancy in cell line models (Ulisse et al., 2007).

**Oncogenesis**
Analysis of differentiated thyroid cancers indicates that TACC3 mRNA levels were either upregulated (44%) or downregulated (56%) in tumors, in some cases correlation was observed between TACC3 and Aurora-A kinase (Ulisse et al., 2007). However protein analysis was not reported.

**Breakpoints**

**Note**
Rearrangements of the human TACC3 gene have not been described. However, translocation breakpoints in the WHSC1 gene, associated with multiple myeloma upregulate the intact TACC3 promoter (Stewart et al., 2004). Tacc3 in the mouse genome is a site of proviral integration of MoMuLV transmitted via milk from infected mothers. This leads to upregulation of the gene and leads to the development of lymphomas (Chakraborty et al., 2008).

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