Atlas of Genetics and Cytogenetics in Oncology and Haematology

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Gene Section

Review

TOPORS (topoisomerase I binding, arginine/serine-rich)

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Identity

Other names: EC 6.3.2.-; LUN; OTTHUMP00000021182; OTTHUMP00000021184; OTTHUMP00000045227; P53BP3; RP31; TP53BPL; p53BP3

HGNC (Hugo): TOPORS

Location: 9p21.1

DNA/RNA

Description

Spans approximately 8kbs of DNA in the reverse strand of chromosome 9.

Transcription

Two splicing variants.
Transcript 1 (ENST00000360538): Transcript length 4145 bps, three exons, first one non-coding.
Transcript 2 (ENST00000379858): Transcript length 3,621 bps, two exons, first one non-coding.

Pseudogene

None reported.

Protein

Description

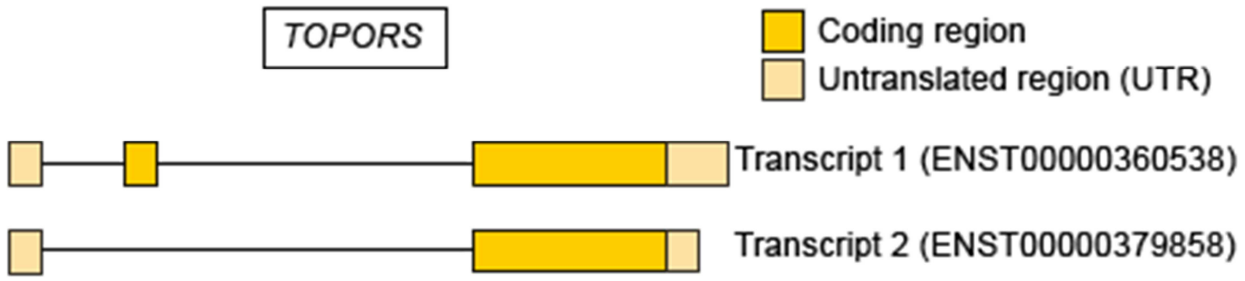
TOPORS transcript 1 encodes a protein containing 1,045 amino acids (ENSP00000353735).
TOPORS transcript 2 encodes a protein containing 980 amino acids (ENSP00000369187).
The 1045aa human TOPORS contains a RING family zinc-finger domain and a leucine zipper (LZ) domain in the N-terminal. It also possesses a C-terminal bipartite nuclear localization signal (NLS), five sequences rich in proline, glutamine, serine and threonine (PEST sequences) and an arginine rich domain.

Expression

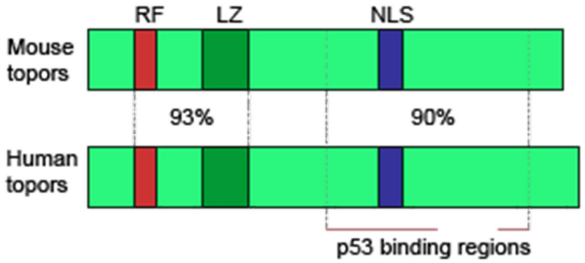
Widely expressed.

Localisation

Nucleus.



The two splicing variants of TOPORS are shown. Transcript 1 (ENST00000360538) has three exons, the first one non-coding. Transcript 2 (ENST00000379858) has two exons, the first one non-coding. The coding regions are shown in yellow boxes and the non-coding regions (untranslated regions, UTRs) are shown in open boxes.



Homology between murine Topors and human TOPORS is shown. The N-terminal Ring-finger (RF, red) and leucine zipper (LZ, green) domains show 93% homology and the C-terminal nuclear localization signal (NLS, blue) domain shows 90% homology between mouse and human. The P53 binding regions of TOPORS, located inside the NLS domain, are highlighted with red lines.

Function

The RING finger protein TOPORS contains a RING family zinc-finger domain, a putative leucine zipper (LZ) domain, five sequences rich in proline, glutamine, serine and threonine (PEST sequences), an arginine/serine (RS) domain and a bipartite nuclear localization signal (NLS). TOPORS was first identified as a human topoisomerase I-interacting protein by yeast two-hybrid screening (Haluska et al., 1999). TOPORS is localized in the nucleus and has been reported to be closely associated with the PML bodies (Weger et al., 2003; Rasheed et al., 2002). An important role of TOPORS is its ability to interact with the tumor suppressor protein P53 (Zhou et al., 1999). Forced expression of murine Topors during DNA damage stabilizes p53, enhances the p53-dependent transcriptional activities of waf1, MDM2 and Bax promoters and elevates the level of endogenous $p21^{waf1}$ mRNA (Lin et al., 2005). These findings suggest an anti-oncogenic role for TOPORS. Indeed, it was shown that TOPORS expression is decreased or undetectable in colon adenocarcinomas relative to normal colon tissue, and the protein level of TOPORS is undetected in several colon cancer cell lines (Saleem et al., 2004). Repression of TOPORS expression was also reported in progression and development of non-small cell lung cancer (Oyanagi et al., 2004).

Furthermore, loss of heterozygosity in the region 9p21, the chromosomal locus harboring TOPORS, has been frequently associated with different malignancies (Puig et al., 2005). A high-resolution genomewide mapping study identified deletion of the TOPORS genomic locus in human glial tumors, suggesting a possible role for TOPORS in gliomagenesis (Bredel et al., 2005). A missense mutation in the TOPORS gene was implicated in autosomal dominant pericentral retinal dystrophy, showing that mutations in the TOPORS gene can lead to genetic disorders (Selmer et al., 2009). Concomitant with these observations, point mutations and small insertions and deletions in the TOPORS gene was found to cause approximately 1% of autosomal dominant retinitis pigmentosa (Bowne et al., 2008). Another study reported that mutations in TOPORS cause autosomal dominant retinitis pigmentosa with perivascular retinal pigment epithelium atrophy (Chakarova et al., 2007).

Valuable information on the cellular roles for TOPORS came through several biochemical studies. It was shown that in the nucleus TOPORS undergoes SUMO-1 modifications (Weger et al., 2003). Interestingly, TOPORS itself has the ability to sumoylate other proteins by functioning as a SUMO-1 E3 ligase. For example, TOPORS can sumoylate p53 and the chromatin modifying protein Sin3A (Shinbo et al., 2005; Weger et al., 2005; Pungaliya et al., 2007). Furthermore, TOPORS induce the accumulation of polysumoylated forms of DNA topoisomerase I in vitro and in vivo (Hammer et al., 2007). Intriguingly, apart from its role as a SUMO-1 E3 ligase, TOPORS can also function as an E3 ubiquitin ligase. In fact, TOPORS was the first example of a protein that possesses dual-roles as an E3 ligase for sumoylation and ubiquitination of other proteins. It was reported that Topors works as an E3 ubiquitin ligase with specific E2 enzymes to ubiquitinate the p53 protein and the prostrate tumor suppressor protein NKX3.1 (Rajendra et al., 2004; Guan et al., 2008). Intense investigations have been undertaken in recent years to elucidate the mechanisms of molecules that have dual E3 ligase activities for sumoylation and ubiquitination such as TOPORS. These studies have discovered a new family of proteins, designated as the small ubiquitin-related modifier (SUMO)-targeted ubiquitin ligases (STUbLs), which directly links sumoylation and ubiquitination (Perry et al., 2008). It has been suggested that similar to STUbLs, TOPORS may be recruited to its targets through SUMO-associated interactions and stimulate their ubiquitination in a RING finger-dependent manner (Perry et al., 2008).

Furthermore, TOPORS has been connected with transcriptional regulation because of its role as an E3 ubiquitin ligase. In drosophila, the homolog of human TOPORS (dTopors) ubiquitinates the Hairy transcriptional repressor, suggesting that TOPORS could be involved in regulating other transcription factors as well (Secombe et al., 2004). Indeed, it was shown that TOPORS interacts with the adeno-associated virus type 2 (AAV-2) Rep78/68 proteins and enhances the expression of a Rep78/68 dependent AAV-2 gene in the absence of the helper virus (Weger et al., 2002). Finally, it was shown that drosophila dTopors was required for the nuclear organization of a chromatin insulator, suggesting a role for TOPORS in regulation of the chromatin (Capelson et al., 2005).

Homology

Widely conserved among different species. Murine Topors shows high similarity with human TOPORS.

Mutations

Germinal

TOPORS has been implicated in autosomal dominant pericentral retinal dystrophy (adPRD), an atypical form of retinitis pigmentosa. Retinitis pigmentosa is the collective name for a group of genetically induced eye disorders that are frequenctly associated with night blindness and tunnel vision. The TOPORS gene was sequenced in 19 affected members of a large Norwegian family. A novel missense mutation, c.1205a>c, resulting in an amino acid substitution p.Q402P, was found in all of the cases. Furthermore, the mutation showed complete co-segregation with the disease in the family, with the LOD score of 7.3. This mutation was not detected in 207 unrelated and healthy Norwegian subjects (Selmer et al., 2009). A separate study showed that mutations in the TOPORS gene are responsible for autosomal dominant retinitis pigmentosa (adRP). Mutations that included an insertion and a deletion were identified in two adRP-affected families (Chakarova et al., 2007). Finally, another recent study investigated whether mutation(s) in the TOPORS gene is associated with autosomal dominant retinitis pigmentosa (adRP). The frequency of TOPORS mutation was analyzed in an adRP cohort of 215 families and two different mutations, namely, p.Glu808X and p.Arg857GlyfsX9, were identified. This study concluded that point mutations and small insertions or deletions in TOPORS may cause approximately 1% of adRP (Bowne et al., 2008).

Implicated in

Non-small cell lung cancer (NSCLC)

Disease

Non-small cell lung cancer (NSCLC) is the major form of lung cancer, with a frequency of 80~90% of all lung carcinomas. NSCLCs are usually classified into three groups, namely, squamous cell carcinoma, adenocarcinoma and large-cell carci-noma. The squamous cell carcinoma is linked with smoking and accounts for approximately 25~30% of all lung cancers, which are usually found in the middle of the lungs or near a bronchus. Adenocarci-noma is frequently spotted in the outer part of the lungs and is thought to be responsible for ~40% of all lung cancers. About 10~15% of lung cancers are large-cell carcinomas, which can start in any part of the lung and has the ability to grow and spread quickly, making this type of lung cancers difficult to treat.

Oncogenesis

Expression of TOPORS was found to be signifi-cantly repressed in lung cancer tissues compared to normal lung tissues. TOPORS gene expression was slightly down-regulated along with progression of primary tumors, and strongly downregulated along with nodal metastases. Interestingly, in normal tissues TOPORS gene expression was down-regulated in smokers (Oyanagi et al., 2004). These findings show that there is a reverse correlation between NSCLC and TOPORS expression and suggest that TOPORS may act as a tumor sup-pressor gene for lung cancers.

Glial brain tumor

Disease

Glial brain tumors arise from glial cells and are highly lethal. Glial brain tumors include astrocytomas, oligodendrogliomas and oligoastro-cytomas.

Oncogenesis

A recent study investigated copy number alterations of 42,000 mapped human cDNA clones in a series of 54 gliomas of varying histogenesis and tumor grade by comparative genomic hybridization technology. This study reported a set of genetic alterations predominantly associated with either astrocytic or oligodendrocytic tumor phenotype. Among these genetic alterations, a minimally deleted region containing the TOPORS gene was identified, suggesting a role for TOPORS in gliomagenesis (Bredel et al., 2005).

Colon cancer

Disease

Cancerous growth in colon, rectum or the appendix are collectively addressed as colon cancer or colorectal cancer. This is the third most frequent form of cancer and a major cause of cancer-related death all over the world.

Oncogenesis

TOPORS expression is decreased or undetected in colon adenocarcinomas compared to normal colon tissues. Furthermore, TOPORS protein is not detectable in several colon cancer cell lines, suggesting an anti-oncogenic role for TOPORS (Saleem et al., 2004).

Autosomal dominant retinitis pigmentosa (adRP)

Disease

Autosomal dominant retinitis pigmentosa (adRP) is a form of retinitis pigmentosa, a collective title for a group of genetically induced eye disorders that are frequenctly associated with night blindness and tunnel vision.

Prognosis

Mutations and small insertions or deletions of the TOPORS gene have been associated with adRP. TOPORS has been associated with autosomal dominant pericentral retinal dystrophy (adPRD), which has a favorable prognosis compared to classical retinitis pigmentosa (RP). A novel mis-sense mutation, c.1205a>c, resulting in an amino acid substitution p.Q402P, was observed in all affected members of a large Norweigian family (Selmer et al., 2009). In another study, an adRP cohort of 215 families was investigated and two different mutations, namely,

p.Glu808X and p.Arg857GlyfsX9, were identified (Bowne at al., 2008). TOPORS has also been implicated in autosomal dominant retinitis pigmentosa with perivascular retinal pigment atrophy, a disorder that showed a distinct phenotype at the earlier stage of the disease, with an unusual perivascular cuff of retinal pigment epithelium atrophy, which was found surrounding the superior and inferior arcades in the retina. This study reported mutations in the TOPORS gene that included an insertion and a deletion was identified in two adRP-affected families (Chakarova et al., 2007).

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