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Gene Section
Review

TRAP1 (TNF receptor-associated protein 1)

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Identity

Other names: HSP75, HSP90L

HGNC (Hugo): TRAP1

Location: 16p13.3

Local order: Genes flanking TRAP1 (from telomere to centromere):
- NLRC3: 16p13.3, NLR family, CARD domain containing 3;
- BTBD12: 16p13.3, BTB (POZ) domain containing 12;
- DNASEI: 16p13.3, Deoxyribonuclease I;
- TRAP-1;
- CREBBP: 16p13.3, CREB binding protein;
- ADCY9: 16p13.3, adenylate cyclase 9;
- SRL: 16p13.3, sarcalumenin.

Note: TRAP-1 gene encodes for an intra-mitochondrial protein highly homolog to members of the Hsp90 family which play a fundamental role in protein folding, protein degradation and signal transduction. TRAP1 is highly conserved through evolution, binds ATP and exhibits an ATPase activity that is inhibited by both geldanamycin and radicicol.

DNA/RNA

Description

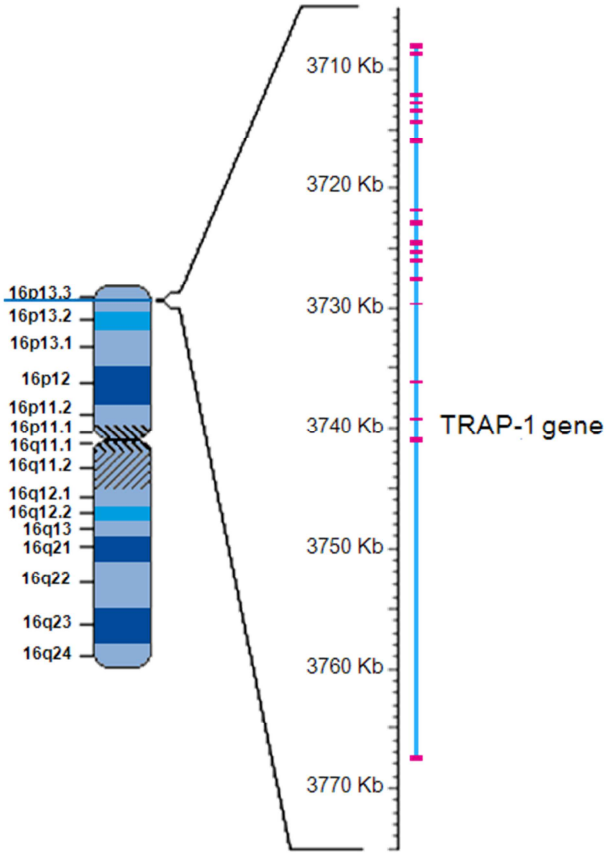
According to the NCBI map viewer, TRAP1 gene maps to NC_000016.9 and encompasses about 60 Kb. The gene contains 18 exons.

Transcription

The mRNA is 2263 bp long.

Pseudogene

No TRAP1 pseudogenes were reported in human.

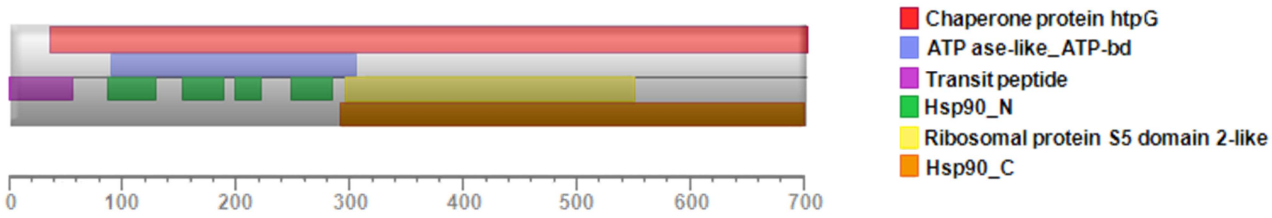


Map of the chromosome 16p13.3 region showing the in scale position of the TRAP1 gene and its organization in exons (purple boxes) and introns (blue lines).

Protein

Description

TRAP1 has a molecular weight of 80110 Da and consists of 704 amino acid residues.



Schematic representation of the domain organization of TRAP1 protein (Data from SwissProt, InterPro, Ensembl).

It contains a N-terminal domain (transit peptide) required for its transport from cytoplasm to mitochondria, a middle domain involved in ATPase activity, a charged domain, and a C-terminal domain. Of note, it lacks the charged domain found immediately after the N-terminal domain in other HSP90 proteins. It contains four ATP binding sites in 119, 158, 171 and 205 position. TRAP1 undergoes to following post translational modifications:
- N6-acetyllysine in 87, 332, 382, 424, 466 position;
- phosphotyrosine in 366 position;
- phosphoserine in 401 position;
- phosphothreonine in 494 position.

Expression

Northern blot analysis has revealed that the protein is expressed, although at different levels, in skeletal muscle, liver, heart, brain, kidney, pancreas, lung and placenta.

Localisation

TRAP1 is located in mitochondria, although immunoelectron microscopy has been provided evidence that it can also be found at specific extramitochondrial sites (pancreatic zymogen granules, insulin secretory granules, cardiac sarcomeres, nuclei of pancreatic and heart cells and cell surface of blood vessel endothelial cells).

Function

TRAP1 binds the intracellular N-terminal half of the tumor necrosis factor receptor (TNFR1) and, thus, it is involved in signal transduction pathways TNFR-1-mediated. Through these pathways TRAP1 up-regulates the expression of different genes, such as those involved in cell cycle, cell motility and metastatic spread. In particular, in the brain the interaction TRAP1-TNFR1 is involved in modulating the expression of the N-cadherin, that is downregulated in TRAP1 knockdown cells, and in regulating the inter-cellular adhesion and synaptic morphology of neuronal cells. TRAP1 interacts, by means of a LxCxE motif, also with the T antigen-binding domain of the retinoblastoma protein (Rb), during the mitosis and after heat shock promoting in vitro the refolding of RB, and with the tumor suppressor EXT1 and EXT2, and the mitochondrial ribosomal protein S12 3'-UTR. In contrast with Hsp90 protein, TRAP1 does not associate with the classic Hsp90 co-chaperones p23 and Hop (p60). Recently, it has been demonstrated that TRAP1 is an in vitro substrate of PARPs (Poly(ADP-ribose) polymerases). PARPs catalyze the transfer of adenine phosphate ribose units from NAD to proteins and are involved in DNA repair, transcription, mitosis and telomere length maintenance.
TRAP1 plays an important role in protecting cells against oxidative stress and apoptosis. To this purpose it has been observed that TRAP1 suppression in mitochondria induces the apoptosis process by means of ROS production. What is more TRAP1 overexpression decreases ROS production and preserves mitochondrial membrane potential during the ischemia-like condition of glucose deprivation and preserves ATP levels and cell viability during oxygen-glucose deprivation. TRAP1 protects cells from granzyme M-mediated apoptosis by preventing the accumulation of ROS. The cleavage of TRAP1 by the granzyme abolishes its antagonistic function to ROS, and leads to ROS accumulation. It has been proposed that mitochondrial homeostasis is differentially regulated in tumor versus normal cells, in part due to elevated expression of TRAP1 in mitochondria. The overexpression of TRAP1 might buffer mitochondrial proteins from direct damage caused by exposure to prolonged oxidative stress. To this regard, it was reported that TRAP1 is a member of a prosurvival mitochondrial pathway highly activated in tumor cells that antagonizes the proapototic activity of cyclophilin D (CypD), a protein involved in the regulation of the mitochondrial permeability transition pore.
TRAP1-overexpression induces a decrease in levels of ROS, Caveolin-1, glutathione peroxidase (GPX), and manganese superoxide dismutase (MnSOD) as well as of the senescence-associated beta-galactosidase in cells treated with deferoxamine (DFO), an iron chelator responsible of mitochondrial dysfunction and senescence-like cellular morphology. It has been shown that TRAP1 is a MYC target, thus it may be considered involved in increased apoptosis in MYC-overexpressing cells and accountable for the elevated susceptibility of such cells to tumor necrosis factor alpha-mediated apoptosis.
Hypoxia conditions induce an up-regulation of protein levels of TRAP1 in osteoarthritic chondrocyte and in cartilage tissue, and in cardiomyocytes, in which TRAP1 plays a protective role by regulating the opening of the mitochondrial permeability transition pore.

TRAP1 is phosphorylated by PINK1, a serine/threonine protein kinase that localizes to mitochondria, and this phosphorylation mediates the PINK1 protective effects against oxidative stress-induced cell death by preventing the release of cytochrome c from mitochondria. PINK1 mutations that cause the Parkinson disease induce a reduced phosporylation of TRAP1 and thus a sensitization of the cells to the lethal effects of reactive oxygen species.
The expression of TRAP1 in heat stress conditions is modulated by the common variability of the mitochondrial DNA. In fact TRAP1 is over-expressed at both mRNA and intra-mitochondrial protein levels in cybrid line harbouring mtDNA of haplogroup H than in the other cybrid lines (lines J, U, X, T).

Homology

- Canis familiaris: TRAP1 (TNF receptor-associated protein 1)
- Pan troglodytes: TRAP1 (TNF receptor-associated protein 1)
- Bos taurus: TRAP1 (TNF receptor-associated protein 1)
- Rattus norvegicus: Trap1 (TNF receptor-associated protein 1)
- Mus musculus: Trap1 (TNF receptor-associated protein 1)

Mutations

Note
Six SNPs in the TRAP1 gene are found associated with neurological diseases. In particular:
- schizophrenia: SNP rs2108430, T/C, intron 3;
- bipolar disorders: SNP rs6500552, T/C, intron 1;
- major depression: SNP rs1639150, T/C, intron 1; SNP rs2108430, T/C, intron 3; SNP rs13926, C/G, exon 9 (R307G); SNP rs1136948, C/G, exon 11 (D395E).

Implicated in

Prostate cancer

Note
It has been shown that TRAP1 is overexpressed at both mRNA and protein level in human primary and metastatic prostate cancer tissues but not expressed in normal prostate or benign prostatic hyperplasia. This up-regulation is also shown in different cell lines such as PC-3, LNCaP, 293, K562 and HeLa. Silencing of TRAP1 gene by siRNAs in prostate cancer cells induces apoptotic cell death thus giving evidence upon an antiapoptotic function of TRAP1. In presence of gamitrinibs, a Hsp90 inhibithor acting as ATPase antagonists that accumulates in the mitochondria of human tumor cell lines causing rapid tumor cell death, it is observed a complete death of prostate cancer cells but not of nontransformed BPH-1 cells. On the other hand, the introduction in these cells of TRAP1 induces the gamitrinibs-mediated cell death. By protein microarray analysis of serum from patients affected by prostate cancer, obtained before and after treatment with GM-CSF secreting whole cell immunotherapy (GVAX® immunotherapy), it was demonstrated an antibody response to TRAP1 in post-treatment samples. In particular, analysis of antibody induction in metastatic, castration-resistant prostate cancer (mCRPC) patients, individuated only from 2 of 3 phase 1/2 studies of prostate cancer immunotherapy (G-9803 and G-0010), revealed an induction of TRAP1 antibody and its association with survival time.

Ovarian cancer

Note
Several studies have identified TRAP1 as a potential target in ovarian cancer. In fact TRAP1 is upregulated in human cisplatin (CCDP)-resistant ovarian tumor cells, in endometrial cancer following progesterone stimulation and in estrogen receptor-positive ovarian cell lines. Moreover the TRAP1 estrogen-induced up-regulation is reversed by the anti-estrogen tamoxifen. For ovarian cancer patients treated with the aromatase inhibitor letrozole, differences in expression levels of TRAP1, such as in aromatase expression, were observed between tumors from responsive/stable patients and tumors from patients whose disease was progressing, using serum levels of CA125 marker as an indicator of response.

Colorectal carcinoma

Note
TRAP1 expression is up-regulated in colorectal carcinoma. In fact TRAP1 levels were increased in HT-29 colorectal carcinoma cells in which, as in other neoplastic cells, the above overexpression is involved in 5-fluorouracil-, oxaliplatin- and irinotecan-resistant phenotypes. Conversely, the inhibition of TRAP1 activity by shepherdin, a TRAP1 ATPase antagonist, has been shown to rescue the resistance to apoptosis induced by oxaliplatin and irinotecan in colorectal carcinoma cells resistant to the single agents. These results suggest that TRAP1 could be a component of a pro-survival pathway responsible for multi-drug resistance.

Nasopharyngeal carcinoma

Note
Microarray analysis carried out by using total RNA from 32 pathologically-confirmed cases of poorly-differentiated nasopharyngeal carcinoma (NPC) and RNA from 24 normal non-cancerous nasopharyngeal tissues (NP) have demonstrated that TRAP1 is up-regulated in NPC compared to NP, thus indentifying this protein as potential candidate biomarker in nasopharyngeal carcinoma.

Lymphoma

Note

In ALK-positive anaplastic large-cell lymphoma, a type of non-Hodgkin lymphoma, the knockdown of TRAP1 determine cell death induced by TRAIL or doxorubicin. Expression levels of TRAP1 has been shown increased in EBV infected B cells and, since this infection resulted in the induction of ROS in Burkitt's lymphoma, it was suggested that over-expression of TRAP1 play a role in the protection of the EBV infected cells against ROS and apoptosis.

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