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Gene Section
Review

C12orf5 (chromosome 12 open reading frame 5)

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Abstract

Review on C12orf5, with data on DNA/RNA, on the protein encoded and where the gene is implicated.

Identity

Other names: FR2BP, TIGAR

HGNC (Hugo): C12orf5

Location: 12p13.32

DNA/RNA

Description

The human TIGAR gene is composed of 6 exons spanning genomic region about 50,4 kb (GenBank NC_000012.11). The transcript mRNA is 8,2 kb (GenBank NM_020375.2) and it is composed by the exon regions 5827..5937, 15914..15951, 21673..21794, 34453..34530, 35901..36011 and 36894..44662.

Transcription

The human TIGAR coding sequence consists of 813 bp from the start codon to the stop codon. There are no splicing variants reported.

Pseudogene

A pseudogene of the ribosomal protein S15 has been located in the region 8981..9473 by computational analysis using a gene prediction method, but there is not experimental data proving it.

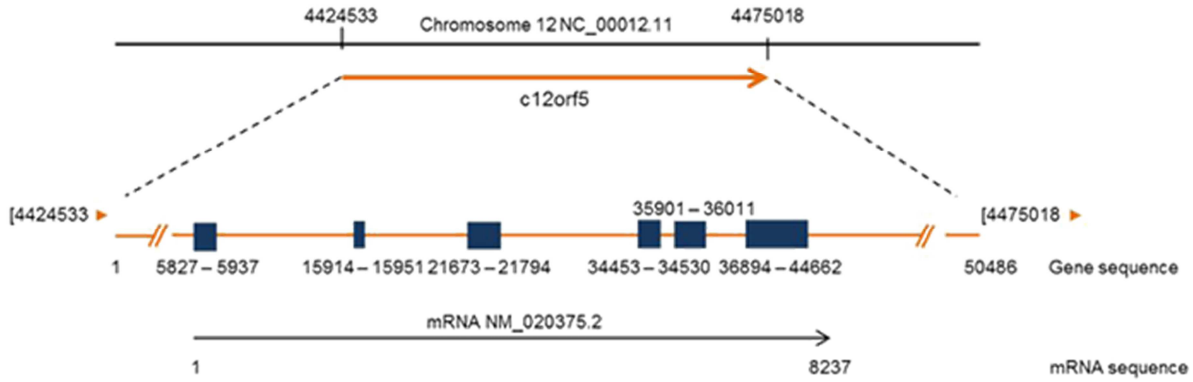

Figure 1. Schematic representation of TIGAR location in chromosome 12, gene structure and transcript mRNA. Different numbering has been used considering chromosomal, gene or mRNA sequence.

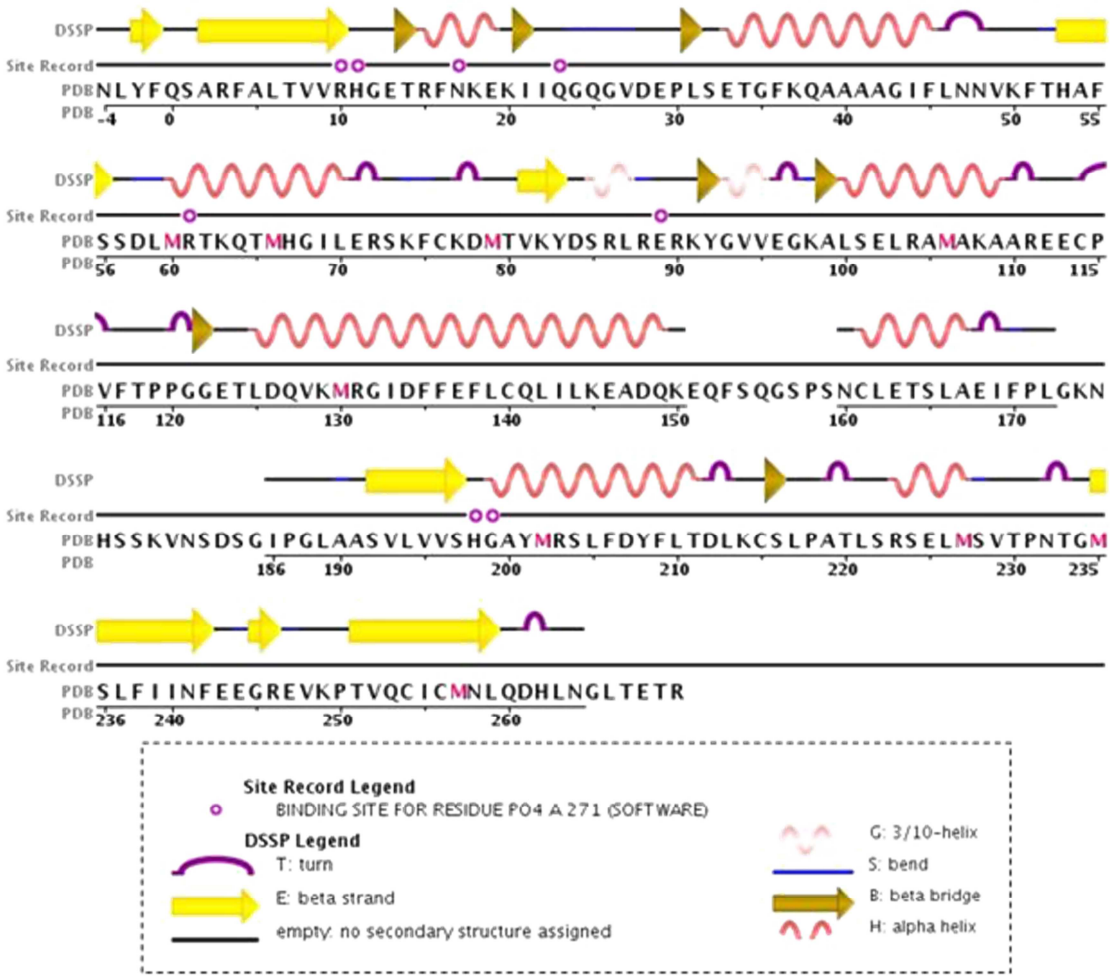

Figure 2. Diagram of TIGAR structure from PDB (entry number: 3DCY). The PDF file does not contain information about the parts of the sequence that are not underlined.

Protein

Description

Human TIGAR protein consists of 270 aminoacids, with a molecular weight of 30063 Da.

It is composed of a bisphosphatase active site in which two histidines, His-11 and His-198, and one glutamic acid, Glu-102, are key residues for its function.

TIGAR catalytic domain belongs to the histidine phosphatase superfamily of proteins, a conserved group of proteins which contain a domain with a histidine forming a phosphoenzyme transiently during the catalysis (Rigden, 2008). This domain shares similarity with enzymes of the phosphoglycerate mutase family (PGAM) and with the bisphosphatase domain of 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase (PFK-2/FBPase-2), in which the three aminoacids in the catalytic domain are conserved.

More information about TIGAR protein can be found in Uniprot Q9NQ88.

Human TIGAR structure contains different motifs as represented in the image below (PDB reference 3DCY).

The crystallized structure of Danio rerio TIGAR is available in PDB (3E9D reference) and was published by Li and Jogl, 2009.

Expression

TIGAR mRNA is expressed in all the tissues in which it has been analysed and it is overexpressed in several cancer cell lines such as T-lymph Jurkat cancer, kidney HEK-293, liver HuH-7 and HepG2, lung A549, colon RKO, bone U2OS, brain GAMG, prostate LnCap, cervix HeLa and breast MCF7.

All this information can be found in GeneCards (sections proteins and expression).

Localisation

TIGAR is mainly localized in the cytoplasm. Under hypoxic conditions, a relocalization of the protein linked to HK-2 (hexokinase 2) in the outer mitochondrial membrane has been described (Mathupala et al., 2009; Cheung et al., 2012).

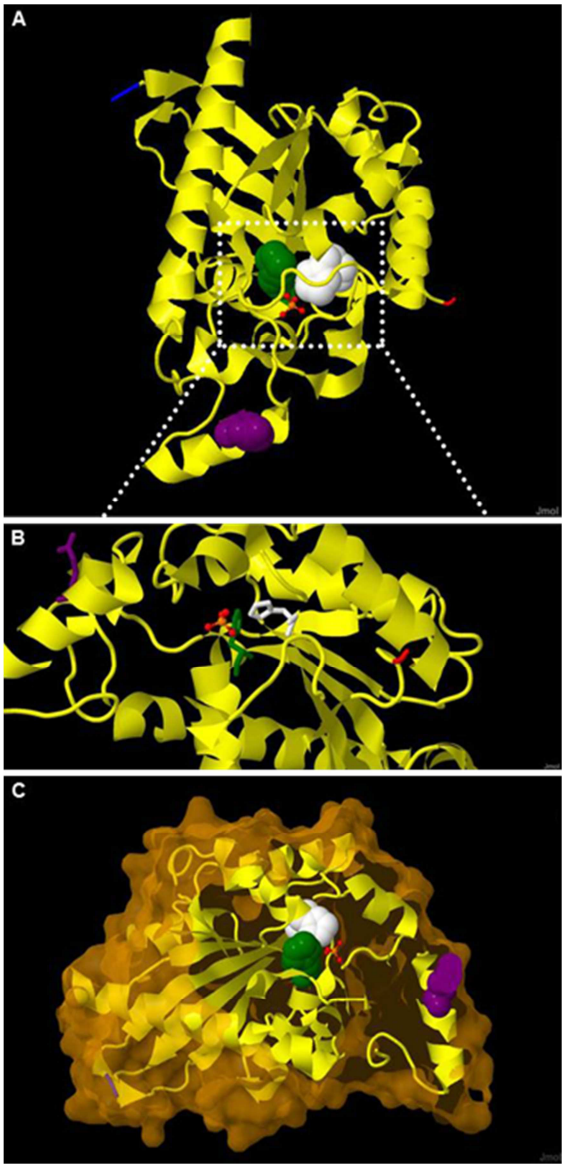

Figure 3. Human TIGAR crystalized structure visualization in Jmol software. His-11 is represented in white, Glu-102 is in purple, His-198 is colored green and C and N terminus are represented in red and blue, respectively. **A)** General protein view. **B)** Zoom of the visualization to the catalytic core, with the two histidines represented and the phosphate group painted following the consensus-based coloring of atoms. **C)** Protein surface and inside-core representation. The central core of the protein is composed by a six-stranded mixed β sheet flanked by α helices on both sides.

Function

TIGAR was identified by microarray analysis of gene expression after TP53 induction (Bensaad et al., 2006). TIGAR plays a role in the TP53 tumor suppressor program by reducing reactive oxygen species (ROS) levels and preventing DNA damage-induced apoptosis. Their functions are based on glycolysis inhibition and the enhancement of pentose phosphate pathway (PPP).

TIGAR is a bisphosphatase that hydrolyzes Fructose-2,6-bisphosphate to Fructose-6-phosphate, which can enter the PPP to generate NADPH and ribose-5-phosphate, thus, reducing oxidative stress and generating nucleotide precursors (Bensaad et al., 2006).

Beta-D-fructose 2,6-bisphosphate + H_2O ⇔ D-fructose 6-phosphate + phosphate

The switch from TP53-induced cell-cycle arrest to apoptosis following maintained stress is associated with downregulation of TIGAR and therefore the loss of P53-dependent survival agents could be the cause of the apoptotic response. It has been proposed that TP53-dependent metabolism regulation could be orchestrated by different mechanisms other than the ones that regulate TP53-induced apoptosis. TIGAR antiapoptotic effects are oxidative-stress dependent. The apoptosis induction by other mechanisms is not affected by TIGAR, as it was shown in IL-3-dependent apoptosis FL5.12 cell line, and in anti-Fas induced apoptosis in U2OS cells, suggesting that TIGAR can modulate apoptosis in a cell-dependent manner (Bensaad et al., 2006).

As described previously, under hypoxic conditions TIGAR is localized in outer mitochondrial membrane. In this situation, it binds together with HK2 to mitochondria (Mathupala et al., 2009) in a HIF1α (hypoxia-inducible factor 1α) dependent manner, and limits ROS levels.

If HK2 is not present, oxidative stress reduction by TIGAR is lower. It has been shown that mutant TIGAR TM (Triple Mutant without enzymatic activity: H11A/E102A/H198A) is able to relocalize to mitochondria in response to hypoxia and, indeed, is able to bind to HK2 in the outer mitochondrial membrane.

Therefore, the maintenance of mitochondrial membrane potential by TIGAR is independent of its bisphoshatase activity. However, the single deletion of four aminoacids in the C-terminus (258-261) avoided TIGAR mobilization to the mitochondria after hypoxia, although its bisphosphatase activity remained unaltered.

The double mutant TM TIGAR/258-261 was not able to reduce ROS levels (Bensaad et al., 2006; Cheung et al., 2012). In conclusion, TIGAR lowers ROS levels both by inhibiting glycolysis and by enhancing an adequate mitochondrial function coupling to HK2.

TIGAR effects have also been related to autophagy as an inhibition of this cell process was described when cells were exposed to stress conditions such as nutrient starvation or metabolic stress, in parallel with an overexpression of TIGAR and a decrease in ROS cell levels. After TIGAR suppression, autophagy was induced to moderate apoptotic response by restraining ROS levels (Bensaad et al., 2009).

The relation between autophagy and apoptosis can be modulated differently depending on the stimulus and cell type.

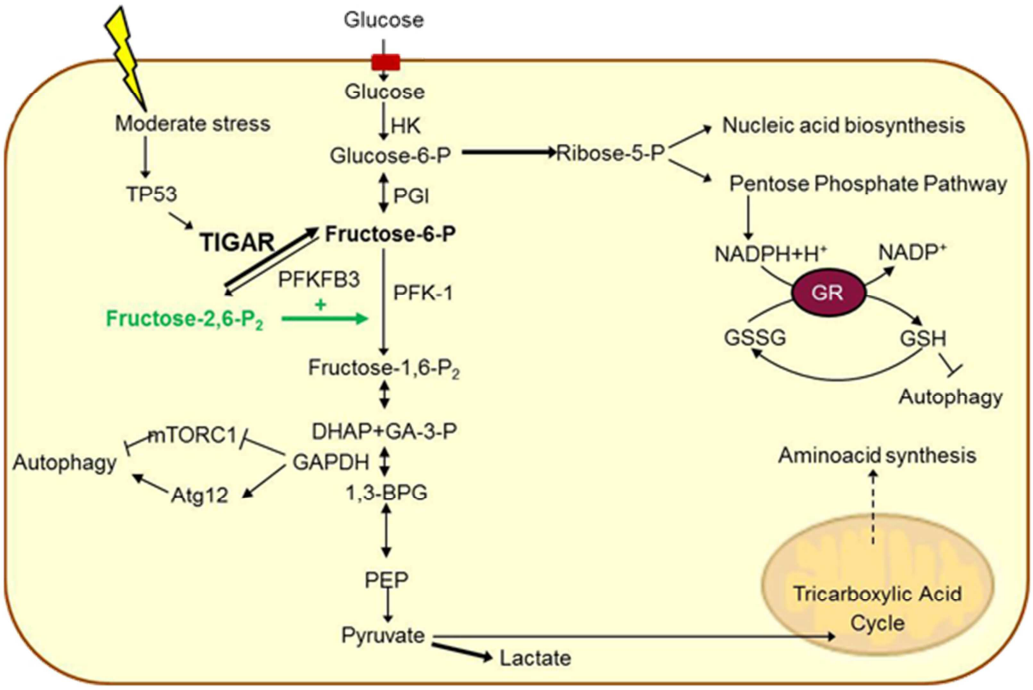

Figure 4. Schematic representation of TIGAR in metabolic pathways. The main enzymes involved in glycolysis are shown, as well as the substrates and products of TIGAR activity. The pentose phosphate pathway and mitochondrial metabolic pathways have been summarized. HK: hexokinase, PGI: phosphoglucose isomerase, PFKFB3: phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3, PFK-1: phosphofructokinase-1, DHAP: dihydroxyacetone phosphate, GA-3-P: glyceraldehyde 3-phosphate, GAPDH: glyceraldehyde 3-phosphate dehydrogenase, 1,3-BPG: 1,3-bisphosphoglycerate, mTORC1: mammalian target of rapamycin complex 1, PEP: phoshoenolpyruvate, GSH: glutathione.

D-galactose (D-gal) treatment of neuroblastoma cells induced necroptosis and autophagy, as shown by upregulation of Bmf, Bnip3, Atg5 and TIGAR, but there were no changes in expression in genes related to apoptosis (Li et al., 2011).

Recently, it has been described a decrease in steady-state mRNA levels of TIGAR when the human hepatocellular carcinoma HepG2 cell line was exposed to high oxidative stress conditions induced by the superoxide radical-generating menadione, hydrogen peroxide (H_2O_2) or nutrient starvation, in parallel with a down-regulation of the damage-regulated autophagy modulator (DRAM). mRNA levels of both genes were recovered when cells were treated with antioxidants such as GSH or N-acetylcysteine, suggesting a complex regulation of tumor suppressor genes by ROS levels (Kim et al., 2013). In front of a disruption in the homeostasis balance of the cell, TIGAR would provide cytoprotection by its antioxidant properties rather than its ability to inhibit autophagy. After a threatening stimulus, a rapid increase in the autophagic flux occurs mostly regulated by post-translational modifications, followed by a transcriptionally-mediated delayed autophagyc response phase, in which TP53 would be activated. In this context, TIGAR would be rapidly transactivated and would mediate its antioxidant response, while autophagy is enhanced by other transcriptionally activated targets, such as DRAM (Pietrocola et al., 2013). Some authors have proposed a TP53-orchestrated mechanism by which this protein would regulate stress-induced autophagy by balancing two proteins with opposite effects: TIGAR and DRAM (Dewaele et al., 2010; Zhang et al., 2010).

In TP53 knock-out mice ($TP53^{-/-}$) cardioprotection against ischemic injury and resistance to cardiac remodeling were observed, and a significant TIGAR overexpression was described. The TIGAR knock-out ($TIGAR^{-/-}$) had the same effects and a TP53-dependent mechanism of autophagy inhibition through the mitophagy enhancer Bnip3 was described. Double knock-out of TP53 and TIGAR mice exposed to ischemia responded with an increase in ROS levels, followed by an overexpression of Bnip3 that lead to mitophagy and, thus, cardioprotection. The activation of Bnip3 and mitophagy was recovered by NAC, confirming that TIGAR-mediated mitophagy inhibition is mediated by ROS. Ventricular remodeling after myocardial infarction is a consequence of both impaired mitochondrial integrity and enhanced apoptosis, whereas mitophagy helps cells to undergo mitochondrial damage and avoid apoptosis, resulting in a diminished initial infarct

size, less ventricular remodeling and restored homeostasis in ischemic myocardium (Kimata et al., 2010; Hoshino et al., 2012).
The analysis of lung tissues from idiopathic pulmonary fibrosis patients revealed decreased autophagyc activity, evidenced by less LC3 and p62 expression. When these cells were treated with TGFβ in vitro, impairment in autophagy was observed, in parallel with an increase in TIGAR expression, although the possible mechanism connecting TGFβ and TIGAR was not described (Patel et al., 2012).
In a co-culture system, Martinez-Outschoorn et al. showed that oxidative stress-induced autophagy correlated with Cav-1 downregulation in cancer associated fibroblasts, and with overexpression of TIGAR in adjacent cancer cells. Consequently, autophagy cancer associated fibroblasts provide recycled nutrients for cancer cell metabolism and, moreover, prevent cancer cells death by upregulating TIGAR and thus conferring resistance to apoptosis and autophagy (Martinez-Outschoorn et al., 2010).
Further studies by the same group demonstrated that the metabolic coupling between cancer cells and fibroblasts can explain tamoxifen resistance as cancer associated fibroblasts enhance the activity of TIGAR in cancer cells, providing protection against tamoxifen-induced apoptosis, which was much higher in monocultures of cancer cells alone (Martinez-Outschoorn et al., 2011). In another study, glutamine was described as a needed factor for Cav-1 downregulation in cancer associated fibroblasts and for the decrease in autophagy mediators and markers in cancer cells, establishing a model in which autophagy fibroblasts may serve as a source of glutamine to fuel cancer cell mitochondrial activity. Therefore, a cycle between catabolic tumor stroma cells and anabolic tumor cells has been proposed to explain the relations between cells in tumor environment (Ko et al., 2011).
Besides, TIGAR has also been proposed to be an anticancer therapy target gene considering that autophagy inhibition in cancer cells would probably increase cell death (Dodson et al., 2013).
All these studies confirm that TIGAR functions are not only restricted to glycolysis regulation, as this protein plays key roles in different cell processes involving oxidative stress restriction.

Activation and regulation

TIGAR belongs to that group of TP53 target genes that become rapidly activated by low levels of stress. There are two possible TP53 binding sites in TIGAR gene: one upstream of the first exon (BS1) and one within the 1st intron (BS2), which is the most efficient one and has been validated by chromatin immunoprecipitation (ChIP) analysis (Bensaad et al., 2006).
In an experimental approach, TIGAR was induced by Actinomycin D and Adriamycin (Bensaad et al., 2006), two well-known activators of TP53, and also by Nutlin-3a, an antagonist of Mdm2 (Hasegawa et al., 2009). Other stimuli that have been described to trigger TIGAR expression are radiotherapy (Peña-Rico et al., 2011), glutamine (Ko et al., 2011), chemotherapy (Madan et al., 2012), UV light (Madan et al., 2012), TNFα and radiotherapy mimetics (Sinha et al., 2013).
When DNA damage occurs, TP53 is expressed either to repair DNA or lead the cell towards apoptosis. High ROS levels can compromise DNA stability which, in turn, could help cells to accumulate mutations and become tumorigenic. As TIGAR reduces ROS levels, it has been proposed as a tumor suppressor gene, although it should be taken into account that, as TIGAR can help tumor cells survival, it could act as an oncogene in some situations. TP53 is able to suppress tumor development when mechanisms of apoptosis, senescence and cell-cycle arrest are impeded. This supports the idea that metabolism, and thereby TIGAR, has a key role in cancer development (Li et al., 2012; Valente et al., 2013).
TIGAR expression can also be modulated in a TP53 independent manner, as results from studies with the TP53 null T98G and H1299 cell lines suggest (Bensaad et al., 2006; Peña-Rico et al., 2011). The mechanisms implicated in the regulation of TIGAR expression in the absence of TP53 are unclear. The CRE-binding protein (CREB) has been described to regulate TIGAR expression through a CRE-binding site at the TIGAR promoter, which was first annotated by bioinformatic analysis and then confirmed by electrophoretic mobility shift assay (EMSA) and ChIP. CREB knockdown reduced enhanced promoter activity and TIGAR expression; whereas CREB overexpression resulted in enhanced promoter activity and TIGAR expression levels (Zou et al., 2013).
Another transcription factor, SP1, was found to bind to TIGAR promoter in a SP1-binding site located in a very short region (-56/-4) both in vitro and in vivo, and was considered a key factor for proper basal activity of TIGAR promoter (Zou et al., 2012).
Recently, some authors have identified HIF-1α as a potential regulator of SCO2 and TIGAR gene expression suggesting the involvement of P300/CBP-associated factor (PCAF) in differential recruitment of HIF-1α and p53 to the promoter of TIGAR and/or SCO2 genes in response of hypoxia in tumoral cells (Rajendran et al., 2013).

Chromosomal rearrangements: copy number variants

Some alterations affecting TIGAR genome region have been described in patients, some of them showed phenotypic effects.

Gain of 12:189578-34178209 resulted in hydronephrosis, micrognathia, edema, depressed nasal bridge, tricuspid regurgitation and diaphragmatic eventration.
Patients with gain of 12:189561-41878937 suffered global developmental delay.
The ones with gain of 12:230361-20643702 showed intellectual disability and electroencephalogram with localized low amplitude activity, whereas gain of 12:191619-8327369 resulted in macroencephaly, visual impairment, intellectual disability, muscular hipotonia, and seizures. For more information, see DECIPHER.

Homology

Location in the mouse: chromosome 6, 61.92 cM, 127085116-127109550 bp, complement strand (MGI). For a comparison of the gene among Homo sapiens, mouse, rat, chimpanzee, cattle, rhesus macaque, dog, chicken and zebrafish see MGI.
For all species known gene tree, see: Treefam database.

Specie	Gene	Query cover	E value	Identity
Pan troglodytes	BAC clone CH251-597E5	32%	0.0	93%
Pongo abelii	BAC clone CH276-457P6	27%	0.0	94%
Gorilla gorilla	BAC clone CH277-211C13	26%	0.0	93%
N. leucogenys	CH271-261A22	28%	0.0	93%
Mus musculus	RIKEN library, F630005B03	5%	0.0	93%
Gallus gallus	Ribosomal protein S15	0%	6e-123	86%
Danio rerio	Ribosomal protein S15	0%	2e-80	80%

Figure 5. Orthologs (adapted from BLAST Local Alignment Tool).

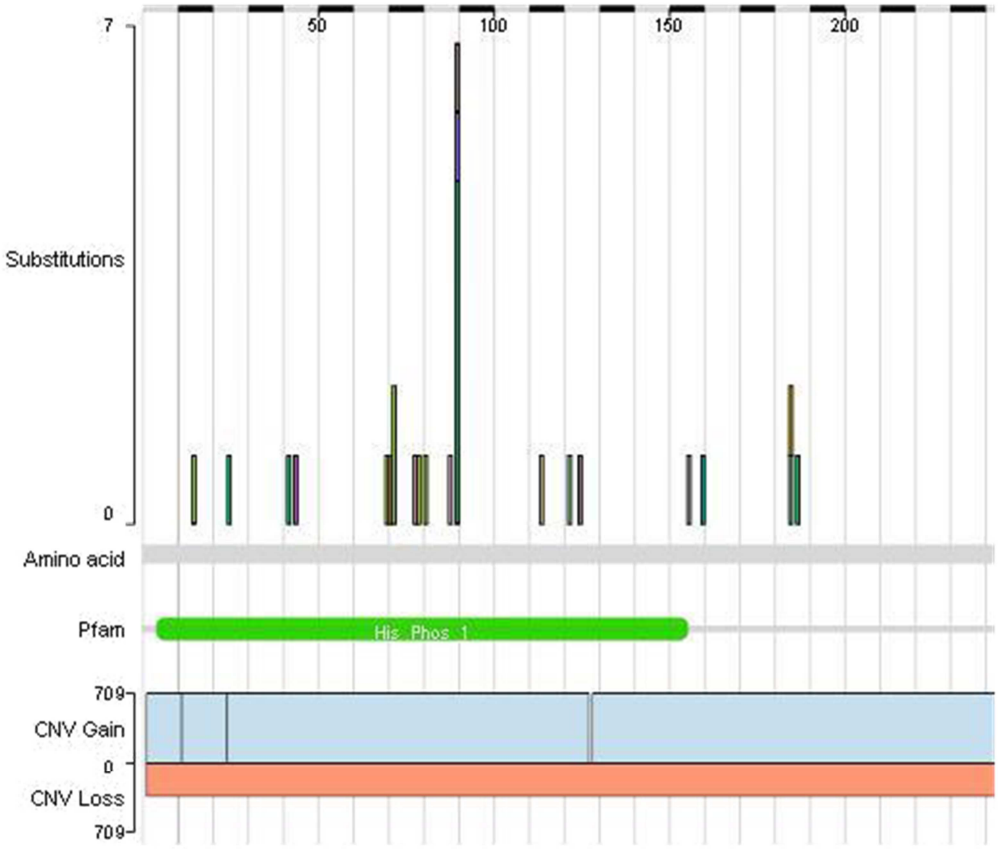

Figure 6. Histogram of mutations found among the aminoacid sequence of TIGAR protein. The maximum number of substitutions at any specific genomic region is represented in Y axis. R90G is the most common aminoacid substitution, caused by 5 different genomic mutations. Histidine phosphatase family homolog domain is represented in green and copy number variants are represented in blue (gain of function) and red (loss of function). Adapted from: COSMIC Database.

Mutations

Note

There have been observed 22 somatic mutations in patient tumor samples collected in the COSMIC database.

Nonsense substitutions: 1, located in c.466G>T (p.G156*).

Missense substitutions: 16, which represent 82% of the mutations described among all patients. Only two missense substitutions have been found in more than one patient: c.268A>G (p.R90G) was found in 5 patients and c.215G>T (p.R72I) was found in 2 patients.

Synonymous substitutions: 4.

No deletions, insertions or chromosomal fusions in TIGAR gene have been described in any tumor sample.

Genomic variants

There are 878 SNP variants described but none of them have clinical significance described (GeneCards).

Implicated in

Various cancers

Prognosis

Despite that little is known about the implication of TIGAR in cancer, there are some authors that point out about the importance of p53 targets such as cytochrome c oxidase 2 (SCO2) or TIGAR in the prognosis of breast cancer patients. Some studies indicated that p53, the most commonly mutated tumor suppressor gene, may have important functions in the regulation of energy-generating metabolic pathways that switch from oxidative phosphorylation to glycolysis via the synthesis of SCO2 and TIGAR (Won et al., 2012).

Oncogenesis

The p53 tumor suppressor pathway coordinates DNA repair, cell-cycle arrest, apoptosis, and senescence to preserve genomic stability and prevent tumor formation. TIGAR has been identified as a p53-inducible gene. TIGAR expression lowers fructose-2,6-bisphosphate levels in cells, resulting in an inhibition of glycolysis and an overall decrease in ROS levels. These functions of TIGAR correlate with an ability to protect cells from ROS-associated apoptosis, and consequently, knockdown of endogenous TIGAR expression sensitizes cells to p53-induced death. Expression of TIGAR may therefore modulate the apoptotic response to p53, allowing survival in the face of mild or transient stress signals that may be reversed or repaired. The decrease of intracellular ROS levels in response to TIGAR may also play a role in the ability of p53 to protect from the accumulation of genomic damage (Bensaad et al., 2006). In an in vitro model of nasopharyngeal cancer, 1-(3-C-ethynyl-beta-d-ribo-pentofuranosyl) cytosine (ECyd), a RNA-nucleoside anti-metabolite with potent anticancer activity, acts by downregulating TIGAR and depleting NADPH. The overexpression of TIGAR was able to rescue cells from ECyd-induced growth inhibition, demonstrating a novel mechanistic action of ECyd on TIGAR. This study suggests a novel link between RNA metabolism and TIGAR regulation (Lui et al., 2010). In human cervical carcinoma cells, RNAi-mediated citrate synthase knockdown accelerated cancer cell metastasis and proliferation being these effects related to deregulation of the p53/TIGAR and SCO2 pathways (Lin et al., 2012). In other studies, TIGAR also mediates de-phosphorylation of RB (retinoblastoma) and stabilisation of RB-E2F1 complex thus delaying the entry of cells in S phase of the cell cycle. Thus, TIGAR inhibits proliferation of cancer cells and increases drug-mediated tumour regression by promoting p53-mediated cell-cycle arrest (Madan et al., 2011; Madan et al., 2012).

Hepatic cancer

Note

Silencing TIGAR by RNAi induces apoptotic and autophagy cell death in HepG2 cells, and this data raise hope for the future successful application of TIGAR siRNA in patients with hepatocellular carcinoma (HCC) (Ye et al., 2013).

Breast cancer

Note

In a model of MCF7 breast cancer cells co-cultured with non-transformed fibroblasts, glutamine protects MCF7 cells against apoptosis, via the upregulation of the anti-apoptotic and anti-autophagic protein TIGAR (Martinez-Outschoorn et al., 2011). The authors showed that glutamine cooperates with stromal fibroblasts to confer tamoxifen-resistance in MCF7 cancer cells (Ko et al., 2011). Moreover, Won et al. (2012) have analysed the expression of p53, SCO2, TIGAR, and COX in 113 cases of invasive breast cancer using immunohistochemistry. A high expression of p53, SCO2, TIGAR, and COX was noted in 27,5% (31 cases), 84,1% (95 cases), 74,3% (84 cases), and 73,4% (83 cases) of the breast tumors, respectively. A high p53 expression was significantly associated with low expression levels of SCO2 ($P = .008$), COX ($P < .0001$), and TIGAR ($P = .007$). These results suggest that p53 can modulate the metabolic pathways via the proteins SCO2 and TIGAR in human breast cancer. TIGAR and p53 can lower the cellular sensitivity to ROS-associated apoptosis, and this potentially contributes to the survival of cells undergoing mild, reversible stress by different anti-tumoral drugs (Won et al., 2012).

Head and neck cancer

Note

In a nasopharyngeal cancer, the onco-protein kinase c-Met maintains TIGAR expression. Inhibition of c-Met resulted in significant downregulation of TIGAR and subsequent depletion of intracellular NADPH. The results provide the first evidence linking c-Met, TIGAR and NADPH regulation in human cancer cells suggesting that inhibition of a tyrosine kinase/TIGAR/NADPH cascade may have therapeutic applicability in human cancers (Lui et al., 2011).

Lung cancer

Note

Sinthupibulyakit et al. (2010) have shown that a glycolytic inhibitor, 2-deoxy-D-glucose (2DG), exhibits a cytotoxic effect on non-small cell lung cancer in a p53-dependent manner. 2DG significantly inhibits ATP production in p53-deficient lung cancer cells (H358) but not in p53-wt cells (A549). This effect is explained by the ROS increase from OXPHOS that induces the expression of p53 antioxidants targets such as cytochrome c oxidase 2 (SCO2) and TIGAR. Therefore, killing of cancer cells by this inhibitor of glycolysis is more efficient in cancer cells without functional p53 that protects against metabolic stress by up-regulation of TIGAR (Sinthupibulyakit et al., 2010).

Other authors point out the importance of autophagy as a cellular homeostatic process to determine cell fate decisions under conditions of stress. Deregulation of autophagy impacts numerous human diseases including cancer and chronic lung diseases. TIGAR could be implicated in the impairment of autophagy by TGF-β(1) and may represent a mechanism for the promotion of fibrogenesis in idiopathic pulmonary fibrosis (Patel et al., 2012).

Intestinal cancer and ulcerative colitis

Note

The ability of TIGAR to contribute to the growth and survival of cells in rapidly proliferating tissue suggested a possible contribution of TIGAR to the development or progression of malignancies. In a mouse model of intestinal tumor induced by deletion of APC in the intestinal stem cells, TIGAR expression was increased and a reduction in tumor development and an enhancement of survival in TIGAR-/- mice were described. Furthermore, using an in vitro organoid culture model, impaired growth of TIGAR-/- cells derived from the crypt of the small intestine was rescued by supplementation with nucleosides and the antioxidant N-acetyl cysteine In the other hand, in a mouse model of ulcerative colitis TIGAR plays an important role in tissue regeneration and that lack of TIGAR results in a failure to repair damaged intestinal epithelium. TIGAR is overexpressed in crypts during the recovery of proliferation in WT mice. The lack of TIGAR results in a failure to repair damaged intestinal epithelium and increase in oxidative damage. In these systems, therefore, TIGAR expression is necessary to maintain normal healthy tissues following stress or damage. Therefore, while loss of TIGAR is deleterious to the recovery from intestinal damage, lack of TIGAR becomes advantageous under conditions where enhanced proliferation occurs in the context of tumor development and progression of malignancies. In conclusion, TIGAR is not required for normal tissue growth and development but becomes important in supporting rapid proliferation in adult intestinal epithelium (Cheung et al., 2013).

Multiple myeloma

Note

Multiple myeloma cells present problems in the expression of oncoprotein MUC1-C. The inhibition of MUC1-C increases ROS and is also associated with down-regulation of TIGAR, resulting in the decrease in NADPH and glutathione (GSH) levels. The suppression of TIGAR and NADPH levels contributes to ROS-mediated apoptosis/necrosis of multiple myeloma cells. These findings indicate that multiple myeloma cells are dependent on MUC1-C and TIGAR for maintenance of redox balance and that targeting MUC1-C activates a cascade involving TIGAR suppression that contributes to multiple myeloma cell death (Yin et al., 2012).

Chronic lymphocytic leukemia

Note

In chronic lymphocytic leukemia a correlation between sensitivity to fludarabine and TIGAR induction mediated by p53 was described. The sensitivity of fludarabine was variable despite all patients analysed had wild type p53 (López-Guerra et al., 2008).

Cervix carcinoma

Note

In human cervical carcinoma cells, RNAi-mediated citrate synthase inhibition accelerated cancer cell proliferation and metastasis in in vitro assays and in vivo tumor xenograft models. The main effects of this knockdown are related with severe defects in respiratory activity and marked decreases in ATP production, but increases in glycolytic metabolism, resulted from deregulation of the p53/TIGAR and SCO2 pathways. This phenotypic change was completely reversed by p53 reactivation suggesting the implication of TIGAR in this malignant proliferation (Lin et al., 2012).

Glioblastoma

Note

Wanka et al. (2012) have shown in glioblastoma that TIGAR is overexpressed and its expression reduces cell death induced by glucose and oxygen restriction. Metabolic analyses reveal that TIGAR inhibits glycolysis and promotes respiration. Further, generation of ROS is reduced whereas levels of reduced GSH are elevated in TIGAR-expressing cells (Wanka et al., 2012). These results agree with the potential of TIGAR as an antitumoral target demonstrated by Peña-Rico et al. (2011), who analysed the effects of TIGAR knockdown in U87MG and T98G glioblastoma-derived cell lines and concluded that TIGAR abrogation provides a novel adjunctive therapeutic strategy against glial tumors by increasing radiation-induced cell impairment, thus allowing the use of lower radiotherapeutic doses. Gliomas are resistant to radiation therapy, as well as to TNFα induced killing. Radiation-induced TNFα triggers Nuclear Factor κB (NFκB)-mediated radioresistance. The existence of ATM-NFκB axis that regulates the metabolic modulator TIGAR suggests its implication in the mechanisms through which inflammation could affect resistance and adaptation to radiomimetics despite concurrent induction of death (Sinha et al., 2013).

Recently, in a neuroblastoma SH-SY5Y cell model a novedous sonodynamic therapy has been assayed. This noninvasive modality for cancer treatment is based on the selective activation of a sonosensitizer agent by acoustic cavitation. The activated sonosensitizer agent might generate reactive oxygen species leading to cancer cell death. This therapy showed a significant decrease in SH-SY5Y cell proliferation in vitro in two and three-dimensional neuroblastoma models and this effect was accompanied by a significant decrease in the TIGAR mRNA expression 24 hours after sonodynamic treatment (Canaparo et al., 2013).

Alzheimer's disease and neurodegeneration

Note

Some authors reported that TIGAR protein levels were decreased in various stages of Alzheimer's disease dementia severity, suggesting diminishing effect of ATM-p53 signalling in counteracting cell death induced by glycolysis/OXPHOS. The progressive decrease of TIGAR expression reported agrees with the findings of altered post-translational modification of TP53, which result in increased formation of functionally inactive TP53 monomers and dimers, but not functionally active TP53 tetramers in Alzheimer's disease patients' brains (Di Domenico et al., 2009; Katsel et al., 2013). Moreover, the reported elevated expression of conformationally altered unfolded TP53 in peripheral blood cells from patients with Alzheimer's disease (Uberti et al., 2008) raises the question of the impact of protein structural changes on the TP53 activity during progression of dementia. TP53 activates TIGAR under low levels of stress. However, following extended exposure to stress and the induction of the TP53-mediated apoptotic response, TIGAR expression is reduced, suggesting that the induction of the apoptotic response may reflect the loss of protection by the TP53-inducible survival signals (Bensaad et al., 2006). Therefore, TIGAR may play a critical role in the switch of TP53-induced responses to stress and a decrease in its expression may have negative consequences for the survival of cells during progression of dementia (Madan et al., 2012).

Diabetes and obesity

Note

Studies performed in rats with diabetes mellitus to evaluate the potential role of p53 and its transcriptional targets in exercise-induced mitochondrial adaptation in skeletal muscle showed a decrease in p53 and TIGAR protein levels, indicating that exercise training can attenuate oxidative stress and increase mitochondrial DNA content in skeletal muscle. Agreeing with these results, suppression of p53 and TIGAR expression could play a role in preventing oxidative stress in insulin resistance (Qi et al., 2011).

In the same direction Derdak et al. (2011) reported that susceptibility to ethanol-induced liver damage in different rat strains and the promotion of insulin resistance is correlated with p53 activation and the activation of TIGAR.

To be noted

Conclusion: In summary, since TIGAR was discovered in 2006 as a p53 target activated in response to moderated stress, several functions related to its fructose2,6-bisphosphatase activity have been described. TIGAR has become a key protein in the regulation of cell processes such as apoptosis, autophagy, DNA repair and control of oxidative stress, determining the fate of the cell in response to different insults. The role of TIGAR in maintaining tumor cell survival is highlighted by the fact that some tumor types have elevated levels of TIGAR expression (Wanka et al., 2012; Won et al., 2012) and the inhibition of different therapeutic targets is associated with a decrease of TIGAR expression. TIGAR can helps to support tumorigenesis by limiting ROS and providing precursors for nucleotide synthesis. These data predict that inhibition of TIGAR may carry therapeutic advantage in cancer treatments as demonstrated in different cancer models (Peña et

al., 2011; Martinez-Outschoorn et al., 2011; Cheung et al., 2013).

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