Atlas of Genetics and Cytogenetics in Oncology and Haematology

OPEN ACCESS JOURNAL AT INIST-CNRS

Gene Section
Review

TIAM1 (T-cell lymphoma invasion and metastasis 1)

Michèle J Hoffmann, Rainer Engers

Institute for Pathology, Heinrich-Heine University, Moorenstr. 5, 40225 Duesseldorf, Germany (MJH, RE)

Published in Atlas Database: August 2008

Online updated version : http://AtlasGeneticsOncology.org/Genes/TIAM1ID42557ch21q22.html
DOI: 10.4267/2042/44518

Identity

Other names: FLJ36302; TIAM-1

HGNC (Hugo): TIAM1

Location: 21q22.11

Local order: The human gene maps to chromosome 21q22.1; between markers D21S298 and D21S404.

Gene orientation: forward strand.

Note

Rho-like GTPases belong to the Ras superfamily and have crucial roles in many cellular processes, such as regulation of the actin cytoskeleton, cell migration, cell cycle progression, gene transcription and cell adhesion. Rho-like GTPases cycle between a GDP-bound inactive form and a GTP-bound active form and activation is catalysed by guanine nucleotide exchange factors (GNEFs) (Minard et al., 2004). The GNEF Tiam1 has been identified as an invasion- and metastasis-inducing gene in a murine T-lymphoma cell line and specifically activates the Rho-like GTPase Rac. Tiam1/Rac signaling controls the establishment and maintenance of E-cadherin-based cell-cell adhesions and loss of Tiam1 leads to epithelial-mesenchymal transition (EMT). Consequently, Tiam1/Rac signaling affects cell migration, invasion and tumor metastasis, but to some extent these effects seem to be cell type- and tumor type-dependent (Ellenbroek et al., 2007). Moreover, Tiam1 and Rac have been implicated in oncogenic transformation of cells.

DNA/RNA

Note

The ensemble database shows five Tiam1 transcripts, only one of which is encoding for the full length protein. Two transcripts are not translated and two others encode only for parts of the Tiam1 protein.

Description

The Tiam1 gene consists of 29 exons encoding for a 7200 bp transcript.

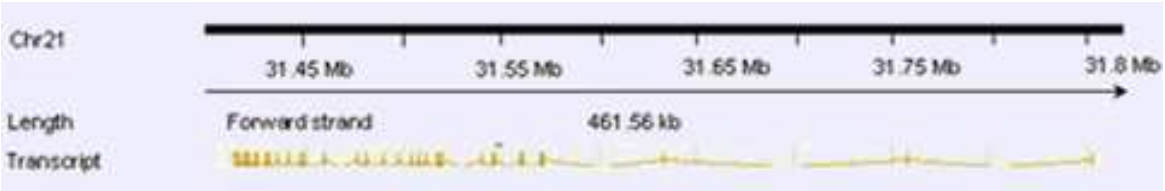
Transcription

Tiam1 is expressed in almost all adult tissues with highest expression levels in brain and testis. Tiam1 is also expressed during embryogenesis as Tiam1 mRNA is detectable from day 10 onwards in mice.

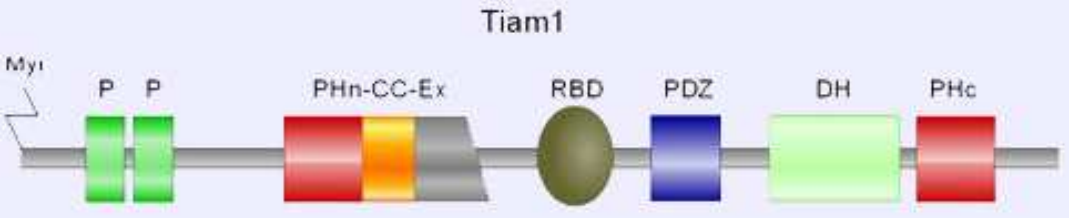
Protein

Note

The human Tiam1 gene encodes a protein of 1,591 amino acids with a predicted molecular mass of 177 kD and several distinct domains.



Localisation of the Tiam1 gene on human chromosome 21 and exon structure.



Domain structure of the Tiam1 protein. Myr, myristoylation site; P, PEST sequence; PHn, N-terminal Pleckstrin homology domain; CC, coiled-coil region; Ex, extended structure; RBD, Ras-binding domain; PDZ, PSD-95/DlgA/ZO-1 domain; DH, Dbl homology domain; PHc, C-terminal Pleckstrin homology domain. PI, phospho-inositides.

Description

The Tiam1 protein is myristoylated at its N-terminus and contains 2 N-terminal PEST domains, an N-terminal pleckstrin homology domain (PHn), a coiled-coil region with adjacent sequence (CC-Ex), a Ras-binding domain (RBD), a PSD-95/DlgA/ZO-1 domain (PDZ) and a catalytic Dbl homology (DH)-PH (PHc) combination. While the PHn-CC-Ex domain of Tiam1 is crucial for membrane localisation of the protein, the DH-PHc combination is characteristic for all members of the Dbl-like family of guanine nucleotide exchange factors (GNEFs) (Engers, 2009).

Expression

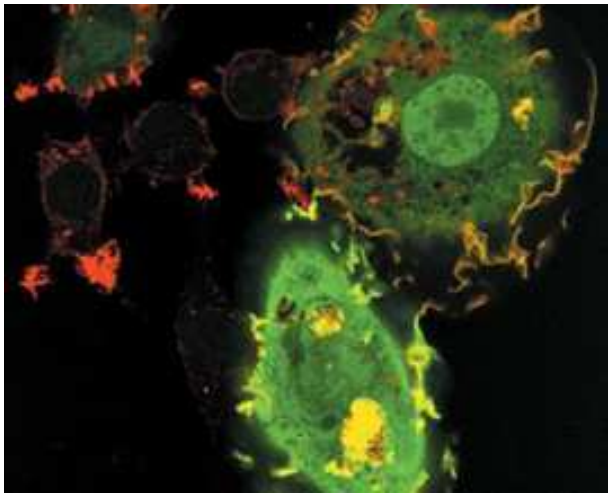
Tiam1 is ubiquitously expressed with highest expression levels in brain and testis. Accordingly, many different cell lines have been shown to express Tiam1 on the RNA and/or protein level.

Localisation

Tiam1 is primarily located in the cytoplasm of cells, but upon activation it is translocated to the plasma membrane. The activity of Tiam1 is regulated by different mechanisms: relief of intramolecular inhibition, post-translational modifications (e.g. threonine phosphorylation) and interaction with other proteins, including Nm23-H1, c-Myc, CD44, Ankyrin, Spinophilin, JIP2/IB2, Par3, Arp2/3, Ras, Trk-B, Rac, phospho-inositides (Mertens et al., 2003; Minard et al., 2004; Engers, 2009).

Function

Tiam1 is a specific activator of the Rho-like GTPase Rac and is implicated in the regulation of different cell biological functions, including cell polarity, adhesion, migration, invasion, metastasis and carcinogenesis. Originally, Tiam1 has been identified as a gene that confers an invasive and metastatic phenotype to otherwise noninvasive murine T-lymphoma cells. In contrast, Tiam1 inhibits migration and invasion of epithelial cells by promoting E-cadherin-mediated cell-cell adhesion and by shifting the balance between distinct invasion-promoting matrix metalloproteinases (MMP-2 and -9) and invasion-inhibiting tissue inhibitors of metalloproteinases (TIMP-1 and -2) towards the TIMPs. However, in other studies
Tiam1 was shown to promote migration and invasion of epithelial cells. These seemingly opposing effects of Tiam1 on migration and invasion in epithelial cells depend at least partly on the cell type studied, the fact as to whether or not the cell substrate used affects the formation of E-cadherin-mediated cell-cell adhesion, and the relative levels of Rac and Rho. Aside from these functions Tiam1 has also been implicated in the development of malignant tumors either as a mediator of oncogenic Ras-signaling (in skin tumors) or as a Wnt-responsive gene (in intestinal tumors) (Engers, 2009).
Morphologically, overexpression of Tiam1 in different cell types induces a distinct phenotype, characterised by large flat cells with epithelioid or sickle-shaped morphology and extensive membrane ruffling. In addition, many of these Tiam1-transfected cells are either polynucleated or contain large numbers of pinocytic vesicles (Minard et al., 2004). Mutational analysis revealed that the PHn-CC-Ex domain is required for membrane localisation of the protein and Tiam1-induced membrane ruffling.



Characteristic phenotype of Tiam1-transfected cells as determined by confocal laser scanning microscopy: In comparison to untransfected control cells (left) Tiam1-transfected cells (right) are large, epithelioid and exhibit pronounced membrane ruffling (green, Tiam1; red, F-actin; yellow, colocalisation of Tiam1 with the actin cytoskeleton).

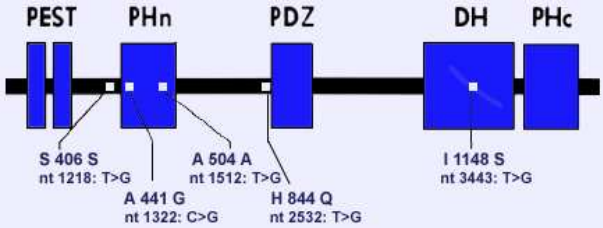
Homology

95% identical to the mouse homolog, Tiam1 is conserved among vertrebrates. Still life (SIF) is the Drosophila homologue of Tiam1.

Mutations

Note

Investigations on mutations in the Tiam1 gene have only been reported in human renal-cell carcinomas.



Domain structure of the Tiam1 protein and localisation of observed mutations (courtesy Engers et al., 2000).

Germinal

None reported.

Somatic

A study on human renal cell carcinomas (RCCs) reported up to five different point mutations in RCC cell lines (Engers et al., 2000). One of these mutations (A441G) was located in the N-terminal PH domain, which is essential for membrane localisation and functional activity of Tiam1. This mutation was found in 11.5% of primary human RCCs, but not in the corresponding normal kidney tissues. Stable overexpression of A441G-Tiam1 proved to be sufficient for oncogenic transformation of NIH 3T3 cells in vitro.

Implicated in

Prostate Cancer

Disease

Tiam1 protein expression was investigated by immunohistochemistry in prostate carcinomas. Tiam1 was found to be significantly stronger expressed in preneoplastic high grade prostate intraepithelial neoplasia (HG-PIN) and prostate carcinomas when compared to corresponding benign secretory epithelial cells (Engers et al., 2006).

Prognosis

Strong overexpression of Tiam1 in prostate cancer is significantly correlated with disease recurrence, the presence of lymph vessel invasion and high Gleason scores. In univariate analysis strong overexpression (e.g. ≥ 3.5-fold) of Tiam1 in prostate cancer predicted significantly decreased disease-free survival as compared to prostate cancer with weak (e.g. <3.5-fold) Tiam1 overexpression. Most importantly, this prognostic effect of strong Tiam1 overexpression remained significant in multivariate analysis, in which all well established prognostic factors in prostate cancer (e.g. preoperative PSA levels, pT stage, Gleason score) were included.

Oncogenesis

Observations that significantly increased Tiam1 expression was not only found in prostate cancer, but also in almost all analysed preneoplastic HG-PIN lesions, suggest that increased Tiam1 expression occurs early in prostate carcinoma development. As a consequence increased Tiam 1 expression might induce transcription of oncogenes or inhibit transcription of tumour suppressor genes, thus contributing to oncogenic transformation.

Colon Carcinoma

Disease

Malliri et al. (2006) identified that Tiam1 is a Wnt-responsive gene which is upregulated in human colon adenomas and implicated in intestinal tumorigenesis. By comparing APC mutant Min (multiple intestinal neoplasia) mice expressing or lacking Tiam1, they found that Tiam1 deficiency significantly reduces the formation and growth of polyps in vivo. In line with this, knock-down of Tiam1 in human colorectal cancer cells inhibited cell proliferation as well as the ability of these cells to form E-cadherin-based adhesions. In already established tumors, the role of Tiam1 still has to be clarified. On the one hand Tiam1 appears to have protective effects as adenocarcinomas arisen in Tiam1-deficient mice were found to be more aggressive than those arisen in Tiam1 wild-type mice (Malliri et al., 2006). On the other hand overexpression of Tiam1 in SW480 colon cancer cells induced a metastatic phenotype, hence more aggressive behaviour of these cells (Minard et al., 2005).

Oncogenesis

Malliri et al. (2006) report a cross-talk between Tiam1/Rac and the canonical Wnt-signaling pathway that affects intestinal tumor formation and progression.

Renal cell carcinoma

Disease

In renal cell carcinoma (RCC) cell lines Tiam1 expression was shown to be inversely correlated with in vitro invasiveness (Engers et al., 2000). In line with this, overexpression of Tiam1 or overexpression of constitutively active V12-Rac1 significantly inhibited migration and invasion of human RCC cells. While the effects on migration were largely dependent on E-cadherin-mediated cell-cell adhesion, inhibition of invasion resulted mainly from selective upregulation of TIMP-1 and TIMP-2 (Engers et al., 2001).

Oncogenesis

In a cohort of different human RCC cell lines and primary RCCs up to 5 different point mutations of the Tiam1 gene were found (Engers et al., 2000). One of these mutations (A441G) was found in
11.5% of primary human RCCs, but not in the corresponding normal kidney tissues. By

overexpression of mutated A441G-Tiam1 in NIH 3T3 cells this mutation was shown to be sufficient for oncogenic transformation in vitro. These data suggest that distinct mutations of the Tiam1 gene might be implicated in the development of a subset of human RCCs.

Skin tumors

Disease

Malliri et al. (2002) investigated the role of the Rac activator Tiam1 in Ras-induced skin tumours in mice. Similar to their reports about the implication of Tiam1 in colon cancer, they found a reduced tumour burden and growth in Tiam1-deficient mice. The reduced tumor growth rate in Tiam1-deficient mice may be a result of increased apoptosis and reduced cell proliferation during initiation. Studies in Tiam1 heterozygous mice suggested that the Tiam1 gene dose affects the efficiency of Ras-dependent tumor initiation. These findings indicate the implication of Tiam1 in Ras-induced skin tumour initiation. However, similar to colon cancer, after tumour initiation Tiam1 expression seems to protect from malignant progression. Thus, the small number of tumours that arose in Tiam1-deficient mice acquired a more aggressive phenotype than tumours arisen in wild-type mice.

In line with this, Uhlenbrock et al. (2004) reported inhibition of migration and invasion by Tiam1 in metastatic melanoma cells. Tiam1 overexpression resulted in gain of cell-cell junctions that counteracted cell motility and invasion.

Oncogenesis

A role for Tiam1 in Ras-induced skin tumour formation has been described by Malliri et al. (2002) (see above).

Retinoblastoma

Disease

Adithi et al. (2006) reported significantly increased Tiam1 expression in invasive retinoblastoma.

Breast Cancer

Disease

Heregulin-beta1 (HRG) promotes motility, scattering and invasiveness of breast cancer cells. Adam et al. (2001) identified Tiam1 as a target of HRG signalling and showed that Tiam1 overexpression mimicks several HRG-induced phenotypic changes in breast cancer cells. In line with these observations, the migratory capacities of several breast cancer cell lines were found to correlate with Tiam1 expression levels (Minard et al., 2004). Moreover, in a small number of breast cancer tissue samples Tiam1 expression was found to correlate with a high tumor grade (Adam et al., 2001).

Pancreatic adenocarcinoma

Disease

In a recent study Cruz-Monserrate et al. (2008) provide evidence that integrin alpha6beta4 promotes the migratory and invasive phenotype of pancreatic carcinoma cells through the Tiam1/Rac pathway in part through upregulation of Tiam1.

Increased vascular permeability

Disease

Reorganization of the cytoskeleton and adhesive complexes provides the basis for increased vascular permeability implicated in various diseases. A recent study of Birukova et al. (2007) demonstrated a role for Tiam1/Rac in HGF-induced endothelial cell barrier protection.

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This article should be referenced as such:

Hoffmann MJ, Engers R. TIAM1 (T-cell lymphoma invasion and metastasis 1). Atlas Genet Cytogenet Oncol Haematol. 2009; 13(7):499-503.