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Gene Section
Review

LATS1 (Large Tumor Suppressor 1)

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Abstract

LATS1 tumor suppressor is a serine/threonine kinase of the AGC kinase family and a core component of the Hippo pathway in mammals. LATS1 regulates various biological processes such as cell cycle progression, genetic stability, cell motility and adhesion, apoptosis, stem cell renewal and differentiation (Visser and Yang, 2010; Mo et al., 2014).
LATS1 performs these functions by phosphorylating various substrates such as transcriptional co-activators YAP and TAZ (Zhao et al., 2007; Hao et al., 2008).
LATS1 is also required for tissue homeostasis in both flies and mice (Visser et al., 2010).
In addition to its roles in a broad spectrum of normal biological processes, loss of LATS1 has been shown to be important for the development of cancer and resistance to chemotherapeutic drugs (Visser et al., 2010).
Therefore, understanding the molecular mechanisms underlying loss-of-LATS1-induced tumorigenesis and drug resistance will shed light on the design of new cancer treatment strategies in the future.

Identity

Other names: Warts

HGNC (Hugo): LATS1

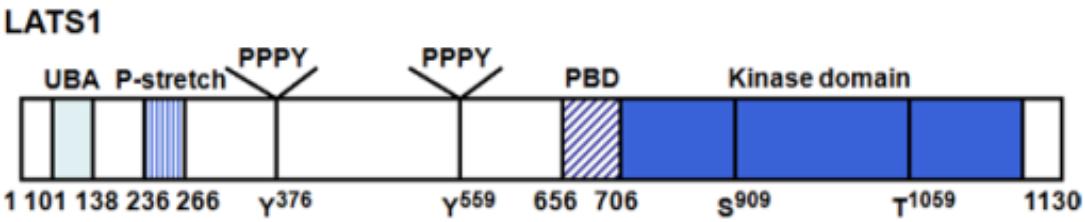
Location: LATS1 is localized to chromosome 6q24-25.1

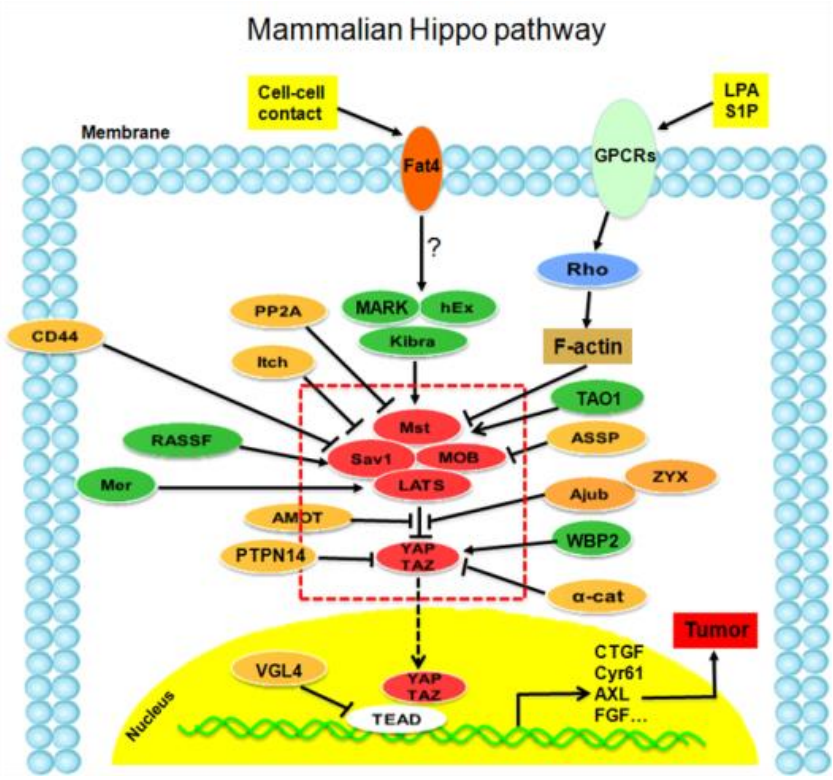
Local order: KATNA1. . LATS1. . LOC645967. . NUP43

DNA/RNA

Description

The LATS1 gene contains 8 exons, ranging in size from 106 bp to 1513 bp. The mRNA transcript spans 4756 bp (NM_004690).





Protein

Transcription

An alternatively spiced variant was identified in vertebrate retina and testis. This smaller variant has deletions of exon 6, 7, and 8 (NM_001270519). Furthermore, a non-coding third transcript variant that is comprised of alternate 5' and internal exons has recently been proposed to exist (NR_073033). In this transcript, an upstream open reading frame (ORF) is predicted to interfere with translation of the longer ORF. The functional significance of these splice variants remains unclear.

Description

LATS1 is a highly conserved Ser/Thr kinase that belongs to the AGC (Protein kinase A/G/C) family of protein kinases.

Within the C-terminal kinase domain lie two conserved residues, Ser909 and Thr1079, which are phosphorylated upon activation.

The N-terminus of LATS1 contains two PPxY motifs, which bind to WW-domain transcriptional co-activators TAZ and YAP or E3 ubiquitin ligases ITCH, WWP1, and NEDD4 as well as a protein binding domain (PBD) that has been shown to bind to MOB1 and cytoskeletal proteins LIMK1 and Zyxin.

In addition, an ubiquitin binding domain (UBA) and a proline-rich region (P-stretch) have been identified in the N-terminal region of LATS1, although the functional significance of these domains has not yet been determined.

Expression

LATS1 is ubiquitously expressed.

Localisation

LATS1 is primarily localized within the cytoplasm, however, LATS1 possesses functions that require its translocation to the nucleus. The mechanism of translocation is not yet understood.

Function

As a tumor suppressor, LATS1 functions as a key regulator of cell cycle progression, apoptosis, and cell migration. As cell cycle regulator, LATS1 is able to modulate multiple aspects of the cell cycle, including G2/M arrest, mitotic exit, activation of the G1 tetraploidy checkpoint, and regulation of cytokinesis. LATS1 also promotes apoptosis by inducing expression of pro-apoptotic proteins BAX, caspase 3 and tumor suppressor p53. Finally, loss of LATS1 has been shown to enhance the rate of cell migration.

HIPPO Signaling Pathway LATS1 is a key player in the conserved Hippo signaling pathway. Core components of this pathway include the adaptor proteins Sav1 and MOB1, which aid in bringing LATS in contact with the kinase MST1/2. MST1/2 can then phosphorylate and activate LATS1. Upstream core components of the Hippo pathway lay FERM domain proteins Willin/FRMD6 and

Merlin/NF2, as well as a protocadherin FAT4 and G-protein-coupled receptor (GPCR) and many other regulators (see Figure). Downstream of LATS1 lay two transcriptional co-activators, YAP and TAZ, which are phosphorylated and inhibited by LATS1, thereby sequestering them in the cytoplasm. Finally, YAP and TAZ have been shown to act through the TEAD/TEF family of transcription factors to modulate the expression of a variety of genes (See Figure). Functionally, the Hippo pathway has been implicated in cell proliferation, apoptosis, the epithelial mesenchymal transition, cell migration, and stem cell differentiation and renewal.

Homology

The LATS1 kinase domain is conserved across species. Human homologs include LATS2 and the nuclear Dbf2-related kinases, NDR1 and NDR2.

Mutations

The Catalogue of Somatic Mutations in Cancer (COSMIC), lists 491 unique mutations in the LATS1 gene. In the COSMIC Cell Lines Project, there are 135 unique mutations in the LATS1 gene listed.

Implicated in

Breast cancer

In breast cancers, loss of heterozygosity is often observed on chromosome 6q suggesting a role for LATS1 in breast cancer carcinogenesis (Morinaga et al., 2000). In a study of breast cancer patients, low LATS1 expression has been associated with a biologically aggressive phenotype (Takahashi et al., 2005). In a study of breast cancer tissues, the LATS1 promoter was found to be hypermethylated in 56.7% (17/30) of tumors causing a significant decrease in LATS1 mRNA expression. In breast cancer patients, decreased LATS1 mRNA expression was associated with large tumor size, lymph node metastasis, and estrogen and progesterone negativity. Thus, loss of LATS1 is associated with poor prognosis in breast cancer.

Cervical cancer

In clinical samples of normal and neoplastic cervix, increased expression of upstream regulator ITCH and decreased expression of LATS1 was associated with transformation of cervical epithelial cells and progression of cervical squamous cell carcinoma (Zhou et al., 2014). In cervical cancer patients high ITCH or low LATS1 expression was associated with increased clinical stage and tumor size. Recently, miRNA-21 (miR-21) was found to regulate LATS1 to promote radioresistance in HR-HPV positive cervical cancer implicating LATS1 in cervical cancer sensitivity to treatment (Liu et al., 2015).

Ovarian cancer

Lats1 deficient mice develop soft-tissue sarcomas as well as ovarian stromal cell tumours (St John et al., 1999). In human ovarian cancer, reduced LATS1 expression has been observed in ovarian serous borderline cystadenomas and ovarian serous carcinoma while the opposite pattern is found in ovarian mucinous borderline cystadenomas and ovarian mucinous carcinoma (Xu et al., 2015). In clear cell carcinoma, LATS1 expression was decreased. In ovarian serous carcinoma (but not in mucinous or clear cell carcinomas), LATS1 expression levels were correlated with disease recurrence, clinical stage and tumor grade.

Renal cell carcinoma

LATS1 mRNA expression is reduced in samples from renal cell carcinoma patients (Chen et al., 2014). In these patients, LATS1 expression was associated with cancer pathological grade and clinical stage. The renal cancer cell line 786-O shows hypermethylation of the LATS1 promoter and pharmacological demethylation of the promoter in 786-O reduced cell proliferation while increasing apoptosis and G1 arrest.

Bladder cancer

A recent study identified 29 total and 18 novel single nucleotide polymorphisms (SNPs) in the LATS1 gene using tissues from urinary bladder or colon cancer patients (Saadeldin et al., 2015). 13 SNPs mapped to intronic and untranslated sequences while 5 SNPs mapped to the coding sequences of LATS1 with 4/5 of these novel SNPs representing missense mutations in the serine/threonine kinase catalytic domain of LATS1. The functional significance of these mutations remains unclear.

Colon cancer

In tissue from patients with colorectal cancer, the LATS1 gene was found to be hypermethylated in 57% (25/44) of cases and this hypermethylation was associated with decreased LATS1 mRNA levels (Wierzbicki et al., 2013). 89.4% (127/142) of all colorectal cancer samples analyzed showed decreased LATS1 mRNA. Another study identified 18 novel SNPs in the LATS1 gene using tissues from urinary bladder or colon cancer patients (Saadeldin et al., 2015). 13 SNPs mapped to intronic and untranslated sequences while 5 SNPs mapped to the coding sequences of LATS1 with 4/5 of these novel SNPs representing missense mutations in the serine/threonine kinase catalytic domain of LATS1. The functional significance of these SNPs remains poorly understood.

Lung cancer

In Japanese lung cancer patients, the LATS1 promoter has been found to be hypermethylated in

79.8% (95/119) of tumors (Sasaki et al., 2010). In this study, the methylation status of the LATS1 promoter was associated with squamous histology and smoking status but not patient survival. In a study of non-small cell lung cancer (NSCLC), LATS1 expression is higher in normal lung tissue than in samples from NSCLC tumors (Lin et al., 2014). Low LATS1 expression in NSCLC patients was associated with higher p-TMN stage, increased lymph node metastasis and shorter overall survival. LATS1 overexpression in NSCLC cell lines reduces cell proliferation and invasion.

Nervous system tumors

LATS1 has been reported to be downregulated in human astrocytomas by promoter hypermethylation (Jiang et al., 2006). In tissues from astrocytomas, 63.66% (56/88) showed hypermethylation of the LATS1 promoter while no methylation of the LATS1 promoter was found in 10 normal brain controls. The LATS1 mRNA level was significantly decreased in hypermethylated astrocytoma tissues compared to unmethylated controls. A similar study has shown that LATS1 is downregulated in gliomas (Ji et al., 2012). In gliomas, decreased LATS1 expression was correlated with higher WHO grade, lower Karnofsky Performance Status and shorter overall survival. Therefore, LATS1 is an independent prognostic indicator for survival of glioma patients. In the glioma cell line U251, overexpression of LATS1 reduced cell proliferation, migration and invasion. Recently, a germline LATS1 mutation (c.286C>T; p.R96W) was identified in a family with Li-Fraumeni syndrome (TP53 germline mutation), a MSH4 germline mutation and multiple cases of nervous system tumours (Kim et al., 2014). Peripheral shwannomas were observed in family members lacking the TP53 mutation but who instead carried mutations in MSH4 and LATS1. To examine how LATS1 might drive sporadic nervous system tumorigenesis, the authors screened 81 sporadic nervous system patients for mutations in the LATS1 gene but only identified one such case (a spinal schwannoma with c.2480delG; p.*R827Kfs*8).

Head and neck squamous cell carcinoma (HNSCC)

LATS1 is one of 15 tumor-related genes that frequently show promoter hypermethylation in HNSCC (Steinmann et al. 2009). Increased methylation of these tumor-related genes is associated with less cellular differentiation and higher tumor stage.

Oral squamous cell carcinoma

A pilot study in India examined the methylation status of the LATS1 gene in tumor samples from 13 patients with oral squamous cell carcinoma (Reddy et al., 2015). 54% (7/13) of tumor samples showed hypermethylation of the LATS1 gene.

Soft-tissue sarcoma

Lats1 deficient mice develop soft-tissue sarcomas as well as ovarian stromal cell tumours (St John et al., 1999).

Further, in multiple subtypes of human soft tissue sarcoma (myxoid liposarcoma, leiomyosarcoma and malignant fibrous histiocytoma), a missense point mutation in LATS1 gene locus and reduced LATS1 mRNA levels have been observed (Hisaoka et al., 2002). This decreased expression was suggested to be the result of promoter hypermethylation.

Nevoid basal cell carcinoma syndrome (NBCCS)

A recent case report describes biallelic disruptions of the LATS1 gene in tissues from a patient with NBCCS (Tate et al., 2014). The authors compared superficial basal cell carcinoma (BCC) cells with more infiltrative BCCs by whole-exome sequencing. The infiltrative but not superficial BCCs showed mutations in the LATS1 gene. Specifically, infiltrative BCCs had one allele with the nonsense mutation c.943C>T (p.Q315X) as well as the loss of the other wild-type allele of LATS1. Loss of heterozygosity analysis showed a deletion in the distal region of chromosome 6q.

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