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Gene Section
Review

SIAH1 (siah E3 ubiquitin protein ligase 1)

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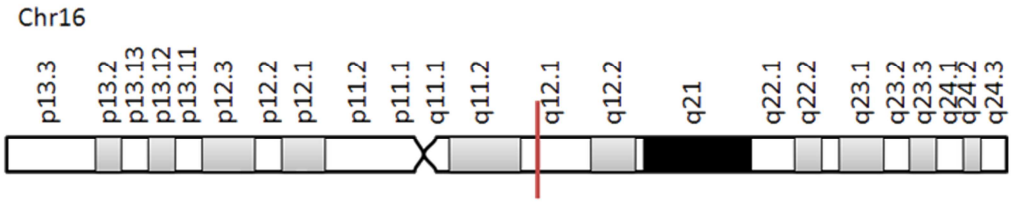
Identity

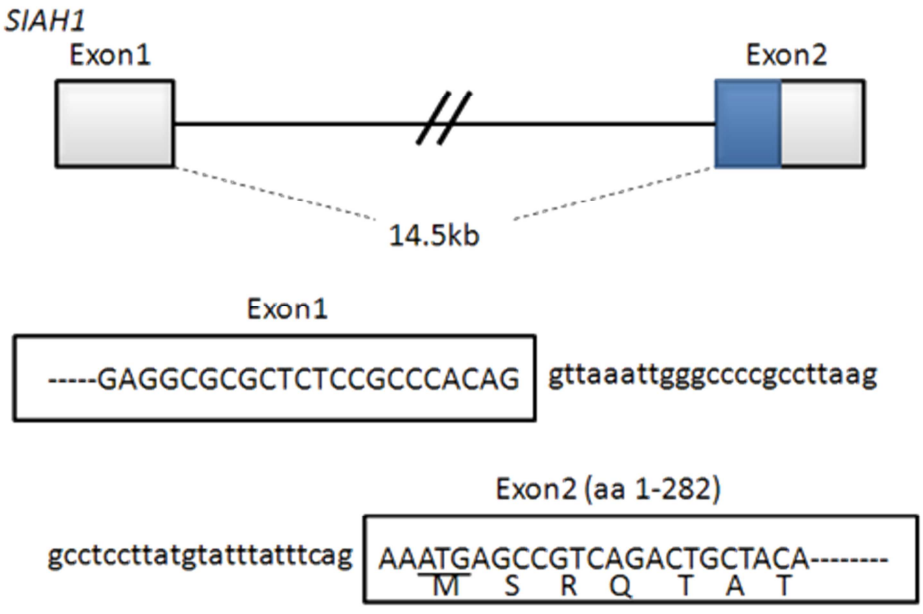
Other names: SIAH1A
HGNC (Hugo): SIAH1
Location: 16q12.1

DNA/RNA

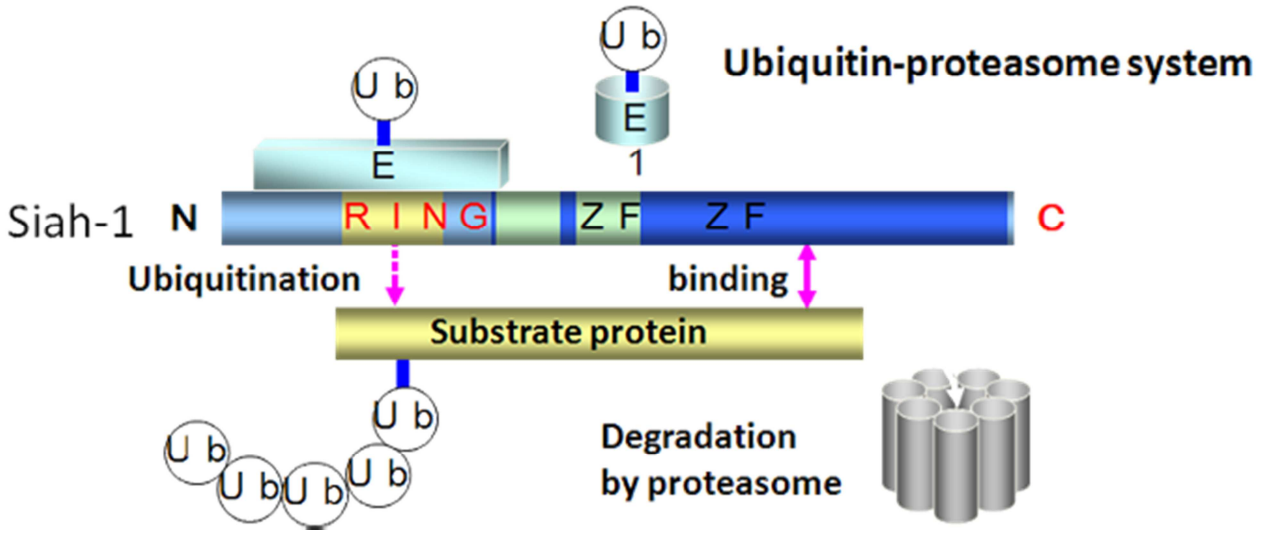
Note
The human Siah1 gene is composed of 2 exons, separated by an intron of roughly 14,5 kb.



Map of chromosome 16 with region 16q12.1 highlighted as the location of the gene SIAH1.



Genomic structure and exon-intron boundaries for SIAH1. The relevant DNA sequences at exon-intron boundaries are indicated, and respective amino acid sequences are indicated below in single-letter code. The entire open reading frame of SIAH1 is in exon 2, and its initiating methionine is underlined.



Schema of Siah1 structure. Siah1 has RING domain at the N-terminus and the substrate binding domain (SBD) at the C-terminus. Some substrate proteins are recognized by this substrate binding domain directly, and receive ubiquitin-conjugation.

Pseudogene

One pseudogene has been reported.

Protein

Expression

Siah1 mRNA is widely expressed in the human tissues. It is expressed at higher level in placenta, skeletal muscle and testis.

Localisation

Siah1 protein can be localized in both cytoplasm and nucleus.

Function

Siah1 is the mammalian homolog of Drosophia seven in absentia (SINA) protein (Carthew and Rubin, 1990). Siah1 protein plays a key role in biological processes such as the cell cycle, programmed cell death, and oncogenesis (Nemani et al., 1996). The Siah family of RING-domain proteins are components of ubiquitin ligase complexes, targeting proteins for proteasomal degradation. Numerous substrates targeted for degradation by Siah proteins have been reported; Synphilin-1 (Nagano et al., 2003), DCC (Hu et al., 1997), N-CoR (Zhang et al., 1998), BOB1/OBF1 (Boehm et al., 2001, Tiedt et al., 2001), c-Myb (Tanikawa et al., 2000), Kid (Germani et al., 2000) and CtIP (Germani et al., 2003). Siah1 expression is upregulated by p53, revealing a link between genotoxic injury and destruction of β-catenin and reduced T-cell factor/lymphoid enhancer factor (Tcf/Lef) activity (Liu et al., 2001; Jansen et al., 2009). Recent paper showed Siah1 expression facilitates ubiquitination and degradation of the tumor suppressor HIPK2 that is a key regulator of the apoptotic programme induced by DNA damage (Winter et al., 2008).

It has been shown that the nuclear translocation and accumulation of GAPDH play important roles in early events leading to cell death initiation and execution (Sirover, 1999), resulting in the various degenerative diseases. Siah1 functions as a potential carrier/shuttle proteins for the induction of GAPDH nuclear translocation because of its nuclear location signal (NLS) domain in Siah1 (Hara et al., 2005).
Siah1a knockout mice are growth-retarded, exhibit early lethality, and display spermatogenetic defects. They also exhibit high numbers of osteoclasts with low numbers of osteoblasts, resulting in severe osteopenia (Frew et al., 2004).

Homology

Human: Siah2.
Mouse: Siah1a, Siah1b, Siah2.

Mutations

Note

There is limited evidence for mutation, with only one report of a low frequency of inactivating mutations in gastric cancer (Kim et al., 2004).

Implicated in

Breast cancer

Note

Wen et al. showed that Siah1 overexpression induced cell apoptosis by up-regulating the level of Bim through the activation of the JNK signaling pathway, and the suppression of Siah1 expression increased cell invasion via the activation of the ERK signaling pathway in breast cancer cells (Wen et al., 2010a; Wen et al., 2010b).
He et al. showed that overexpression of Siah1 enhanced radiation-induced apoptosis in breast cancer cells (He et al., 2010).

Those data suggest that Siah1 can be a novel therapeutic target for tumor cell death.

Leukemia

Note

Krämer et al. showed that the leukemia fusion protein PML-RARα (promyelocytic leukemia-retinoic acid receptor α which causes acute promyelocytic leukemias, is degraded by ubiquitin-proteasome system and that their turnover critically depends on the E2-conjugase UbcH8 and Siah1. They also showed that HDAC inhibitor enhanced the degradation of leukemia fusion proteins via UbcH8-Siah1 axis and could be a new therapeutic strategy for leukemia (Krämer et al., 2008).

Gastric cancer

Note

Kim et al. found two missense mutations in the SIAH1 gene in gastric cancer. The two mutants revealed that impairment of β-catenin degradation pathway, increase of cyclin D1 expression, and inhibition of apoptosis in culture cells, suggesting that mutations of Siah1 gene may play an important role in the development and progression in a subset of gastric cancer through β-catenin stabilization and apoptosis block (Kim et al., 2004).

Hepatocellular carcinoma

Note

Matsuo et al. showed that the expression level of SIAH1 was markedly downregulated in hepatocellular carcinoma (HCC), especially in advanced stages (Matsuo et al., 2003). Okabe et al. showed that the paternally expressed gene 10 (PEG10) was an important factor in HCC progression as a substrate for Siah1 and could be a novel molecular target for treatment (Okabe et al., 2003).

Parkinson's disease

Note

Nagano et al. showed for the first time that Siah1 ubiquitinated α-synuclein-interacting protein, Synphilin-1, leading to degradation. These proteins are located in Lewy body, the pathological hallmark of Parkinson's disease (Nagano et al., 2003). Recent papers showed that Siah1 facilitated mono- or di-ubiquitination of α-synuclein, leading to Lewy body formation (Lee et al., 2008; Rott et al., 2008). But no mutation in Siah1 has been identified in Parkinson's disease patients (Franck et al., 2006).

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