Atlas of Genetics and Cytogenetics in Oncology and Haematology

OPEN ACCESS JOURNAL INIST-CNRS

Gene Section
Review

NUAK1 (NUAK family, SNF1-like kinase, 1)

Fumika Inazuka, Hiroyasu Esumi

Research Institute for Biomedical Sciences, Tokyo University of Science, Japan (FI, HE)

Published in Atlas Database: March 2014

Online updated version : http://AtlasGeneticsOncology.org/Genes/NUAK1ID46275ch12q23.html
DOI: 10.4267/2042/54167

Abstract

Review on NUAK1, with data on DNA/RNA, on the protein encoded and where the gene is implicated.

Identity

Other names: ARK5

HGNC (Hugo): NUAK1

Location: 12q23.3

Note: Details concerning the local order of the human NUAK1 locus can be found at ensembl.org. Human NUAK1 is found on chromosome 12 at position 106457118-106533811. Mouse NUAK1 is located on chromosome 10 at position 84370905-84440597.

DNA/RNA

Description

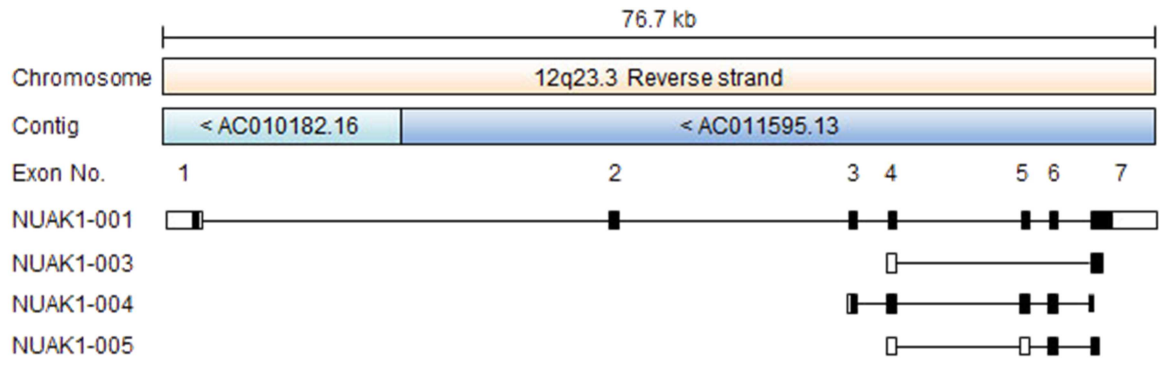
The human NUAK1 gene is composed of seven exons and spans approximately 76.7 kbp of genomic DNA.

Transcription

The human NUAK1 gene encodes a 6828-bp mRNA. The coding region contains 1986 bp. Three short splice variants (547-569 bp) have been reported.

Pseudogene

No pseudogenes are known.



The human NUAK1 gene has four splice variants. NUAK1-001 is composed of seven exons, which spans 6828 bp and encodes a 661-aa protein. NUAK1-003 is composed of two exons including one non-coding exon, which spans 547 bp and encodes a 118-aa protein. NUAK1-004 is composed of five exons, which spans 560 bp and encodes a 152-aa protein. NUAK1-005 is composed of four exons including two non-coding exons, which spans 569 bp and encodes a 74-aa protein (see Ensembl ENSG00000074590). Open boxes indicate untranslated regions and shaded boxes indicate coding regions of the gene.

The catalytic domain of NUAK1 protein is located in the N-terminal at residues 55 to 306. K84 is an ATP binding site. T211 is phosphorylated by LKB1, which activates NUAK1 (Lizcano et al., 2004). W305 is required for binding of USP9X (Al-Hakim et al., 2008). The GILK motif is a direct binding site for protein phosphatase PPP1CB (Zagorska et al., 2010).

Protein

Description

NUAK1 protein consists of 661 amino acids and has a molecular weight of 74 kDa (Nagase et al., 1998). NUAK1 contains a serine/threonine-protein kinase domain at its N-terminus that is conserved among AMPKalphas and AMPK-related kinases (AMPK-RKs) (Manning et al., 2002). The same as the AMPKalphas and most other AMPK-RKs, NUAK1 can be phosphorylated by tumor suppressor LKB1 at a conserved threonine residue (corresponding to Thr-211 in NUAK1) in the T-loop of the catalytic domain, which activates the kinase activity of NUAK1 (Lizcano et al., 2004). The phosphorylation at Thr-211 is prevented by atypical Lys29/ Lys33-linked polyubiquitin chains, which can be removed by the de-ubiquitinating enzyme USP9X (Al-Hakim et al., 2008).

Expression

NUAK1 is preferentially expressed in highly oxidative tissues such as cerebrum, heart, and soleus muscle in human and mouse (Nagase et al., 1998; Inazuka et al., 2012). In mouse embryogenesis, NUAK1 is prominently expressed in the neuroectoderm during neurulation, and in the cerebral cortex after the late embryonic stage (Ohmura et al., 2012; Courchet et al., 2013). In C2C12 mouse myoblasts, NUAK1 is increasingly expressed as the cells differentiate into myotubes (Niesler et al., 2007). The elevated expression of NUAK1 has been observed in clinical samples obtained from colorectal cancers, pancreatic cancers, hepatocellular carcinomas, gliomas, and angioimmunoblastic T-cell lymphomas (Kusakai et al., 2004a; Morito et al., 2006; Liu et al., 2012; Cui et al., 2013).

Localisation

NUAK1 is found in both the cytoplasm and nucleus.

Function

In HEK293 cells NUAK1 phosphorylates myosin phosphatase regulator MYPT1, which inhibits the activity of a MYPT1-PPP1CB phosphatase complex, enhancing cell detachment (Zagorska et al., 2010). In WI-38 fetal lung fibroblasts and MCF10A immortalized mammary epithelial cells NUAK1 phosphorylates the cyclin-dependent protein kinase regulator LATS1, which leads to destabilization of LATS1 and induces aneuploidy, resulting in cellular senescence in a cellular context-dependent manner (Humbert et al., 2010). In A549 lung adenocarcinoma cells NUAK1 acts as a transcriptional coactivator in a complex with LKB1 and a tumor suppressor p53, which induces cell cycle G1 arrest (Hou et al., 2011).

In mice, NUAK1 is essential for closure of the ventral body wall in developing embryos (Hirano et al., 2006). NUAK1 and NUAK2 function in a complementary manner in the apical constriction and apico-basal elongation during early embryogenesis (Ohmura et al., 2012). The LKB1-NUAK1 pathway regulates cortical axon branching by immobilizing mitochondria at nascent presynaptic sites during postnatal neuronal development (Courchet et al., 2013). NUAK1 has a role in the negative feedback regulation of insulin signaling, which is involved in glucose intolerance under high-fat diet conditions (Inazuka et al., 2012). In Caenorhabditis elegans, UNC-82, an ortholog of NUAK1 and NUAK2, maintains the organization of cytoskeletal structure during cell-shape change presumably through phosphorylation of myosin and paramyosin (Hoppe et al., 2010).

Homology

NUAK1 has the highest homology to NUAK2, whose similarity in the protein as a whole is 58%, and 82% in the kinase domain in human. Homo sapiens NUAK1 is 91% similar to Mus musculus NUAK1, 75% similar to Xenopus tropicalis NUAK1, and 65% similar to Caenorhabditis elegans UNC-82.

Mutations

Somatic

A C-to-T transition at residues 661 in the NUAK1 gene that results in a Pro-to-Ser substitution at codon 221 (P221S) has been found in tissue samples from human colorectal carcinomas and melanomas (Cancer Genome Atlas Network, 2012; Krauthammer et al., 2012).

Implicated in

Glioma

Disease

Malignant gliomas are the most common type of primary brain tumor in adults. Glioma cells are highly proliferative, thereby readily invading surrounding brain structures. Thus, complete surgical resection is practically impossible (Stewart, 2002). Glioma infiltration occurs through the activation of matrix metalloproteinases (MMPs). MMPs also exhibit a function in angiogenesis during tumor neovascularization (Forsyth et al., 1999; Das et al., 2011).

Prognosis

Up-regulation of NUAK1 correlates with the World Health Organization grades of glioma ($P < 0.001$). High NUAK1 expression was markedly associated with reduced overall survival in grade II glioma ($P < 0.01$). The median survival time of patients with high NUAK1 expression (18.37 months, 95% confidence interval (CI): 15.95-20.04) was significantly shorter than that of patients with low NUAK1 expression level (43.80 months, 95% CI: 23.47-48.36). The same conclusions were obtained in grades III and IV gliomas, indicating that NUAK1 is a valuable prognostic marker for glioma patients at all disease stages (Lu et al., 2013).

Oncogenesis

In several kinds of glioma cell lines, NUAK1 promotes IGF-1-induced cell invasion, in which NUAK1 mediates cytoskeleton rearrangement through activation of LIMK1 and cofilin and activates MMP-2 and MMP-9 through production of MT1-MMP. Knockdown of NUAK1 reduces brain invasion in mice with glioma xenografts (Lu et al., 2013).

Colorectal cancer (CRC)

Disease

CRC is the third leading cancer and the fourth leading cause of cancer deaths worldwide (Karsa et al., 2010). Various genetic changes, including APC mutation, mismatch repair defects, Wnt-activated alterations, RAF-mediated alterations, and p53 alterations are concurrently observed in CRC. These mutations are interconnected to generate diverse pathways of colorectal tumorigenesis (Conlin et al., 2005; Roh et al., 2010). In addition, MMPs are overexpressed in colorectal tumors and involved in degrading components of the basement membrane during the progression of CRC (Collins et al., 2001; Dragutinovic et al., 2011).

Prognosis

Higher expression of NUAK1 is observed in advanced cases, and much higher expression is observed in liver metastases (Kusakai et al., 2004b; Roh et al., 2010). The expression of NUAK1 is closely associated with that of MMP-2 and MMP-9. Enhanced expression of NUAK1 is more frequent in tumors with RAF-mediated alterations ($P = 0.001$) or crossover pathways carrying both APC/Wnt-activated and mismatch repair/RAF-mediated alterations ($P = 0.003$) than those without them (Roh et al., 2010).

Oncogenesis

Higher NUAK1 expression is concordant with higher invasion activity in human colorectal cancer cell lines (Kusakai et al., 2004a; Kusakai et al., 2004b). Knockdown of NUAK1 suppresses growth of CRC xenografts in mice (Liu et al., 2012).

Hepatocellular carcinoma (HCC)

Disease

HCC is the fifth most common cancer and the third most frequent cause of death of cancer worldwide. Liver resection is considered to be the mainly curative therapy for HCC, with about 50-70% 5-year overall survival after curative hepatectomy. However, the postoperative recurrence rate remains as high as 70-83.7% (Bruix and Sherman, 2005; Llovet, 2005).

Prognosis

In HCC, the high expression of NUAK1 is related to tumor size ($P=0.005$), histological differentiation ($P=0.047$), tumor stage ($P=0.005$), and a significantly poor prognosis. Multivariate analysis identified the level of NUAK1 expression as an independent predictor of the overall survival rate of patients with HCC (Cui et al., 2013).

Oncogenesis

Several cancer cell lines including HCC which are expressed oncogenic levels of MYC establish a dependence on NUAK1 for maintaining metabolic homeostasis and for cell survival, in which NUAK1 restrains mTOR signaling via suppression of proteasomal degradation of AMPKbeta and also maintains expression of mitochondrial respiratory chain complexes. Knockdown of NUAK1 prevents tumorigenesis in MYC-driven mouse models of HCC. Depletion of NUAK1 after tumorigenesis also suppresses tumor growth and provides a survival advantage to the mice ($P < 0.01$) (Liu et al., 2012).

References

Nagase T, Ishikawa K, Miyajima N, Tanaka A, Kotani H, Nomura N, Ohara O. Prediction of the coding sequences of unidentified human genes. IX. The complete sequences of 100 new cDNA clones from brain which can code for large proteins in vitro. DNA Res. 1998 Feb 28;5(1):31-9

Forsyth PA, Wong H, Laing TD, Rewcastle NB, Morris DG, Muzik H, Leco KJ, Johnston RN, Brasher PM, Sutherland G, Edwards DR. Gelatinase-A (MMP-2), gelatinase-B (MMP-9) and membrane type matrix metalloproteinase-1

(MT1-MMP) are involved in different aspects of the pathophysiology of malignant gliomas. Br J Cancer. 1999 Apr;79(11-12):1828-35

Collins HM, Morris TM, Watson SA. Spectrum of matrix metalloproteinase expression in primary and metastatic colon cancer: relationship to the tissue inhibitors of metalloproteinases and membrane type-1-matrix metalloproteinase. Br J Cancer. 2001 Jun 15;84(12):1664-70

Manning G, Whyte DB, Martinez R, Hunter T, Sudarsanam S. The protein kinase complement of the human genome. Science. 2002 Dec 6;298(5600):1912-34

Stewart LA. Chemotherapy in adult high-grade glioma: a systematic review and meta-analysis of individual patient data from 12 randomised trials. Lancet. 2002 Mar 23;359(9311):1011-8

Kusakai G, Suzuki A, Ogura T, Kaminishi M, Esumi H. Strong association of ARK5 with tumor invasion and metastasis. J Exp Clin Cancer Res. 2004a Jun;23(2):263-8

Kusakai G, Suzuki A, Ogura T, Miyamoto S, Ochiai A, Kaminishi M, Esumi H. ARK5 expression in colorectal cancer and its implications for tumor progression. Am J Pathol. 2004b Mar;164(3):987-95

Lizcano JM, Göransson O, Toth R, Deak M, Morrice NA, Boudeau J, Hawley SA, Udd L, Mäkelä TP, Hardie DG, Alessi DR. LKB1 is a master kinase that activates 13 kinases of the AMPK subfamily, including MARK/PAR-1. EMBO J. 2004 Feb 25;23(4):833-43

Bruix J, Sherman M. Management of hepatocellular carcinoma. Hepatology. 2005 Nov;42(5):1208-36

Conlin A, Smith G, Carey FA, Wolf CR, Steele RJ. The prognostic significance of K-ras, p53, and APC mutations in colorectal carcinoma. Gut. 2005 Sep;54(9):1283-6

Llovet JM. Updated treatment approach to hepatocellular carcinoma. J Gastroenterol. 2005 Mar;40(3):225-35

Hirano M, Kiyonari H, Inoue A, Furushima K, Murata T, Suda Y, Aizawa S. A new serine/threonine protein kinase, Omphk1, essential to ventral body wall formation. Dev Dyn. 2006 Aug;235(8):2229-37

Morito N, Yoh K, Fujioka Y, Nakano T, Shimohata H, Hashimoto Y, Yamada A, Maeda A, Matsuno F, Hata H, Suzuki A, Imagawa S, Mitsuya H, Esumi H, Koyama A, Yamamoto M, Mori N, Takahashi S. Overexpression of c-Maf contributes to T-cell lymphoma in both mice and human. Cancer Res. 2006 Jan 15;66(2):812-9

Niesler CU, Myburgh KH, Moore F. The changing AMPK expression profile in differentiating mouse skeletal muscle myoblast cells helps confer increasing resistance to apoptosis. Exp Physiol. 2007 Jan;92(1):207-17

Al-Hakim AK, Zagorska A, Chapman L, Deak M, Peggie M, Alessi DR. Control of AMPK-related kinases by USP9X and atypical Lys(29)/Lys(33)-linked polyubiquitin chains. Biochem J. 2008 Apr 15;411(2):249-60

Hoppe PE, Chau J, Flanagan KA, Reedy AR, Schriefer LA. Caenorhabditis elegans unc-82 encodes a serine/threonine kinase important for myosin filament organization in muscle during growth. Genetics. 2010 Jan;184(1):79-90

Humbert N, Navaratnam N, Augert A, Da Costa M, Martien S, Wang J, Martinez D, Abbadie C, Carling D, de Launoit Y, Gil J, Bernard D. Regulation of ploidy and senescence by the AMPK-related kinase NUAK1. EMBO J. 2010 Jan 20;29(2):376-86

Karsa LV, Lignini TA, Patnick J, Lambert R, Sauvaget C. The dimensions of the CRC problem. Best Pract Res Clin Gastroenterol. 2010 Aug;24(4):381-96

Roh SA, Choi EY, Cho DH, Jang SJ, Kim SY, Kim YS, Kim JC. Growth and invasion of sporadic colorectal adenocarcinomas in terms of genetic change. J Korean Med Sci. 2010 Mar;25(3):353-60

Zagórska A, Deak M, Campbell DG, Banerjee S, Hirano M, Aizawa S, Prescott AR, Alessi DR. New roles for the LKB1-NUAK pathway in controlling myosin phosphatase complexes and cell adhesion. Sci Signal. 2010 Mar 30;3(115):ra25

Das G, Shiras A, Shanmuganandam K, Shastry P. Rictor regulates MMP-9 activity and invasion through Raf-1-MEK-ERK signaling pathway in glioma cells. Mol Carcinog. 2011 Jun;50(6):412-23

Dragutinović VV, Radonjić NV, Petronijević ND, Tatić SB, Dimitrijević IB, Radovanović NS, Krivokapić ZV. Matrix metalloproteinase-2 (MMP-2) and -9 (MMP-9) in preoperative serum as independent prognostic markers in patients with colorectal cancer. Mol Cell Biochem. 2011 Sep;355(1-2):173-8

Hou X, Liu JE, Liu W, Liu CY, Liu ZY, Sun ZY. A new role of NUAK1: directly phosphorylating p53 and regulating cell proliferation. Oncogene. 2011 Jun 30;30(26):2933-42

. Comprehensive molecular characterization of human colon and rectal cancer. Nature. 2012 Jul 18;487(7407):330-7

Inazuka F, Sugiyama N, Tomita M, Abe T, Shioi G, Esumi H. Muscle-specific knock-out of NUAK family SNF1-like kinase 1 (NUAK1) prevents high fat diet-induced glucose intolerance. J Biol Chem. 2012 May 11;287(20):16379-89

Krauthammer M, Kong Y, Ha BH, Evans P et al.. Exome sequencing identifies recurrent somatic RAC1 mutations in melanoma. Nat Genet. 2012 Sep;44(9):1006-14

Liu L, Ulbrich J, Müller J, Wüstefeld T, Aeberhard L, Kress TR, Muthalagu N, Rycak L, Rudalska R, Moll R, Kempa S, Zender L, Eilers M, Murphy DJ. Deregulated MYC expression induces dependence upon AMPK-related kinase 5. Nature. 2012 Mar 28;483(7391):608-12

Ohmura T, Shioi G, Hirano M, Aizawa S. Neural tube defects by NUAK1 and NUAK2 double mutation. Dev Dyn. 2012 Aug;241(8):1350-64

Courchet J, Lewis TL Jr, Lee S, Courchet V, Liou DY, Aizawa S, Polleux F. Terminal axon branching is regulated by the LKB1-NUAK1 kinase pathway via presynaptic mitochondrial capture. Cell. 2013 Jun 20;153(7):1510-25

Cui J, Yu Y, Lu GF, Liu C, Liu X, Xu YX, Zheng PY. Overexpression of ARK5 is associated with poor prognosis in hepatocellular carcinoma. Tumour Biol. 2013 Jun;34(3):1913-8

Lu S, Niu N, Guo H, Tang J, Guo W, Liu Z, Shi L, Sun T, Zhou F, Li H, Zhang J, Zhang B. ARK5 promotes glioma cell invasion, and its elevated expression is correlated with poor clinical outcome. Eur J Cancer. 2013 Feb;49(3):752-63

This article should be referenced as such:

Inazuka F, Esumi H. NUAK1 (NUAK family, SNF1-like kinase, 1). Atlas Genet Cytogenet Oncol Haematol. 2014; 18(11):834-837.