

Gene Section

Mini Review

CENTG1 (centaurin, gamma1)

Chan Chi Bun, Ye Keqiang

Department of Pathology and Laboratory Medicine, Emory University School of Medicine, Atlanta, USA

Published in Atlas Database: May 2007

Online updated version: <http://AtlasGeneticsOncology.org/Genes/CENTG1ID44037ch12q14.html>

DOI: 10.4267/2042/16962

This work is licensed under a Creative Commons Attribution-Non-commercial-No Derivative Works 2.0 France Licence.

© 2007 Atlas of Genetics and Cytogenetics in Oncology and Haematology

Identity

Hugo: CENTG1

Other names: Posphoinositide-3-kinase enhancers (PIKE)-A; AGAP-2; GGAP2; KIAA0167

Location: 12q14.1

DNA/RNA

Description

CENTG1 gene, located on reverse strand, comprises of 18439 bp, which consists of 20 exons and 19 introns.

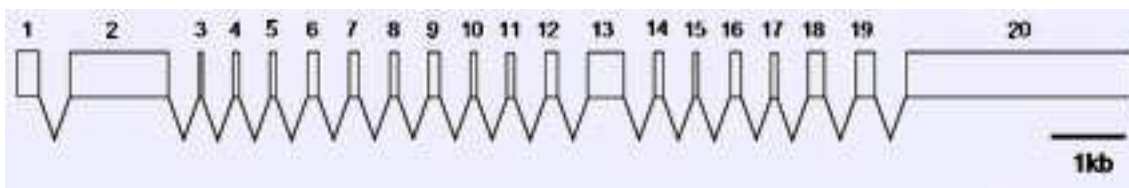
Transcription

Transcription of CENTG1 takes place in a telomeric to

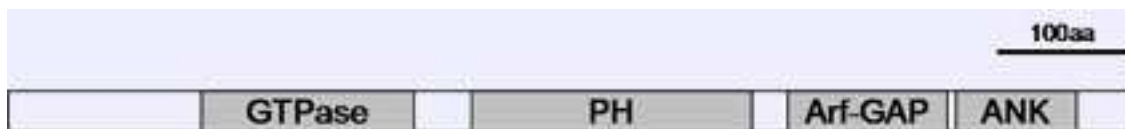
centromere orientation. Two isoforms, namely PIKE-L (3579) and PIKE-A (3938 bp) were identified. No systematic investigations on the production of the two isoforms have been reported but it is suggested that they were produced through alternative splicing and utilization of transcription initiation site. Transcription of PIKE-L begins at exon 2 through 20. Transcription of PIKE-A utilizes another initiation site which begins at exon 1 through 20. Moreover, exon 15 is skipped during the transcription of PIKE-A.

Pseudogene

No pseudogene of CENTG1 has been reported.



Schematic diagram of the CENTG1 gene. The exon numbers are labeled.



Schematic diagram of PIKE-A protein. PIKE-A contains a GTPase domain, a pleckstrin homology (PH) domain, an ADP ribosylation factor-GTPase activating protein (Arf-GAP) domain and ankyrin repeats (ANK).

Protein

Description

PIKE-A proteins contains 836 amino acids (about 91 kDa). It possesses a GTPase domain (aminoacids 143-300), a pleckstrin homology (PH) domain (aminoacids 343-552), an ADP ribosylation factor3 GTPase Activating Protein (Arf-GAP) domain (aminoacids 577-695) and ankyrin repeats (ANK) (aminoacids 702-291). PIKE-A could be cleaved at Asp474 and Asp592 during apoptosis. However, phosphorylation of PIKE-A by Fyn at Tyr682 and Tyr774 protects this apoptotic cleavage.

Expression

PIKE-A mRNA is ubiquitously expressed. Northern blot analysis revealed that the highest expression was found in brain (cerebellum, cerebral cortex, occipital pole, frontal lobe, temporal lobe and putamen) followed by spleen, thymus and periphery blood leukocytes. Detectable amount of PIKE-A mRNA could be found in lung, liver, and small intestine. No signal was detected in heart, placenta, kidney, prostate gland, pancreas, testis, ovary and colon.

Localisation

PIKE-A localizes in both the cytoplasm and the nucleus in COS-7, NIH3T3 and CRL-2061 sarcoma cells. In HEK293 cells, PIKE-A exclusively locates in the cytoplasm. Within the NIH3T3 nucleus, PIKE-A resides in the nucleolus.

Function

PIKE-A is a GTPase that catalyze the bound GTP to GDP. Its intrinsic GTPase activity is regulated by its C-terminal Arf-GAP domain and PI(3,4,5)P3. In the studies aiming at determining the GTPase activity of various PIKE-A domain in vitro, it was found that the GTPase activity of PIKE-A was dampened when the Arf-GAP domain was absence. Further studies revealed that full-length PIKE-A possessed negligible GTPase activity in the absence of phosphatidylinositol lipid which could be enhanced in the presence of PI(3,4,5)P3. It is suggested that phosphatidylinositol lipids may regulate PIKE-A conformation through its PH domain, leading to the C-terminal Arf-GAP domain accessible to its GTPase domain and accelerating its intrinsic GTPase activity.

PIKE-A is also a physiological interacting partner of protein kinase B (Akt). It was reported that PIKE-A specifically interacted with the regulatory domain and partial catalytic domain of activated Akt through its GTPase domain. Moreover, this interaction was guanine nucleotide dependent as the presence of GTPgammaS strongly stimulated their binding. Through interacting with PIKE-A, both basal and growth factor (e.g. EGF) stimulated Akt activity is greatly enhanced. This enhanced Akt activity is not

triggered by uplifting PI3-kinase activity as PIKE-A neither interacts with PI3-kinase nor affects its activity. Instead, PIKE-A maintains and initiates Akt activation directly in both U87MG and LN-Z308 cells.

Overexpression of PIKE-A in U87MG glioblastoma cells promotes cell proliferation and enhances its invasion activity by stimulating Akt activity. In contrast, depletion of PIKE-A decreases U87MG viability upon staurosporine treatment via enhancing apoptosis.

Homology

PIKE-A is a member of gamma subfamily of centaurin GTPase superfamily, which consists of alpha, beta, gamma, and delta subfamilies. Centaurin gamma subfamily has three members which are gamma1 (PIKE-A), gamma2 (CENTG2) and gamma3 (CENTG3). PIKE-A shares only about 56% and 47% amino acid identity with CENTG2 and CENTG3.

Mutations

Germinal

No germinal mutation of CENTG1 has been reported.

Somatic

PIKE-A mutation was observed in bone sarcoma CRL2098 (R182G, V591M and deletion of aa 756-777), neuroblastoma NGP-127 (T232I), glioblastomas M067 (V119A, S666P) and SF188 (A315V, L360E, E431V and N583D). These mutations altered the GTP binding, GTPase activity and cellular localization of PIKE-A. PIKE-A mutant from NGP-127 hydrolyzed GTP into GDP more potently than those from CRL2098, M067 and SF188. On the other hand, GTP binding to PIKE-A is more profound in CRL2098, M067, SF188 mutant than NGP-127 mutant. All PIKE-A mutants showed similar cytoplasmic localization pattern in HEK293 cells under basal condition. However, when the cells were stimulated with EGF, those mutants from CRL2098, M067 and NGP-127 aggregated in perinuclear zone. No such aggregation was detected in mutants from SF188 cells. Furthermore, cellular morphological transformation from regular round shape to spindle-shaped refractile morphology was observed in NIH3T3 cells transfected with PIKE-A mutants derived from M067 and SF188 cells.

Implicated in

Glioblastoma

Cytogenetics

Chromosome 12q13-q15 is frequently amplified in brain tumors. This chromosomal region contains the MDM2, CDK2 and CENTG1 gene. Subsequent studies revealed CENTG1 was substantially amplified in glioblastoma cell line TP366, LN-Z308 and CRL-2061

genome in addition to a normal CENTG1 on chromosome 12. Further, PIKE-A is markedly amplified as double-minute chromatin bodies in SF-188. This amplification occurs in about 16.7% of primary glioblastoma and 11.1% of glioblastoma cell lines.

Oncogenesis

In addition to overexpression in glioblastoma TP366, LN-Z308, CRL2061 and SF188 cells, mutation of PIKE-A is observed in M067 and SF188 glioblastoma. Studies using nontransforming NIH3T3 cells revealed that overexpression of these PIKE-A mutants strongly promoted cell proliferation in an anchorage-independent manner possibly through enhanced Akt activity. In U87MG glioblastoma, which has low PIKE-A expression, overexpression of PIKE-A mutants derived from M067 and SF188 greatly enhanced Akt and ERK phosphorylation, thereby enhancing cell proliferation and invasion, and preventing apoptotic cell death.

To be noted

Note: PIKE-A is overexpressed in human cancers derived from a great variety of tissues including breast, ovary, colon, stomach, lung, kidney, bladder, vulva, uterus, cervix, rectum, testis and skin.

References

Nagase T, Seki N, Ishikawa K, Tanaka A, Nomura N. Prediction of the coding sequences of 40 new genes (KIAA0161-KIAA0200) deduced by analysis of cDNA clones from human cell line KG-1. *DNA Res* 1996;3:17-24.

Elkahloun AG, Krizman DB, Wang Z, Hofmann TA, Roe B, Meltzer PS. Transcript mapping in a 46-kb sequenced region at the core of 12q13.3 amplification in human cancers. *Genomics* 1997;42:295-301.

Xia C, Ma W, Stafford LJ, Liu C, Gong L, Martin JF, Liu M. GGAPs, a new family of bifunctional GTP-binding and GTPase-activating proteins. *Mol Cell Biol* 2003;23:2476-2488.

Ahn JY, Hu Y, Kroll TG, Allard P, Ye K. PIKE-A is amplified in human cancers and prevents apoptosis by up-regulating Akt. *Proc Natl Acad Sci USA* 2004;101:6993-6998.

Ahn JY, Rong R, Kroll TG, Van Meir EG, Snyder SH, Ye K. PIKE (phosphatidylinositol 3-kinase enhancer)-A GTPase stimulates Akt activity and mediates cellular invasion. *J Biol Chem* 2004;279:16441-16451.

Hu Y, Liu Z, Ye K. Phosphoinositol lipids bind to phosphatidylinositol 3 (PI3)-kinase enhancer GTPase and mediates its stimulatory effect on PI3-kinase and Akt signalings. *Proc Natl Acad Sci USA* 2005;102:16853-16858.

Knobbe CB, Trampe-Kieslich A, Reifenberger G. Genetic alteration and expression of the phosphoinositol-3-kinase/Akt pathway genes PIK3CA and PIKE in human glioblastomas. *Neuropath Appl Neurobiol* 2005;31:486-490.

Tang X, Feng Y, Ye K. Src-family tyrosine kinase Fyn phosphorylates phosphatidylinositol 3-kinase enhancer activating Akt, preventing its apoptotic cleavage and promoting cell survival. *Cell Death Differ* 2006;14:368-377.

Tang X, Ye K. PIKE tyrosine phosphorylation regulates its apoptotic cleavage during programmed cell death. *Advan Enzyme Regul* 2006;46:289-300.

Liu X, Hu Y, Hao C, Rempel SA, Ye K. PIKE-A is a proto-oncogene promoting cell growth, transformation and invasion. *Oncogene* 2007;in press.

This article should be referenced as such:

Chi Bun C, Keqiang Y. CENTG1 (centaurin, gamma1). *Atlas Genet Cytogenet Oncol Haematol*.2007;11(4):297-299.
