

Gene Section

Mini Review

RAP1GAP (RAP1 GTPase activating protein)

Zixing Chen, Xuejun Shao

Jiangsu Institute of Hematology, 1st Affiliated Hospital, Soochow University, Suzhou 215006 JS, China
(ZC, XS)

Published in Atlas Database: January 2010

Online updated version : <http://AtlasGeneticsOncology.org/Genes/RAP1GAPID42043ch1p36.html>

DOI: 10.4267/2042/44888

This work is licensed under a Creative Commons Attribution-Noncommercial-No Derivative Works 2.0 France Licence.
© 2010 Atlas of Genetics and Cytogenetics in Oncology and Haematology

Identity

Other names: RAPGAP; RAP1GA1; KIAA0474; RAP1GAP1; RAP1GAPII

HGNC (Hugo): RAP1GAP

Location: 1p36.12

Local order: From centromere to telomere: NBPF3, ALPL, RAP1GAP, USP48, HSPG2.

DNA/RNA

Description

25 exons encompassing about 73 kb of genomic DNA.

Transcription

About 3.334 kb mRNA, and has three transcript variant, RAP1 GTPase activating protein isoform a, b, c.

Protein

Description

663 amino acids; homodimer and heterodimer with RAP1B.

Expression

Significant expression seen in the brain, kidney and pancreas. Abundant in the cerebral cortex and expressed at much lower levels in the spinal cord. Not detected in the lymphoid tissues. (according to Swiss-Prot).

Localisation

Golgi apparatus membrane; Peripheral membrane protein (according to Swiss-Prot).

Function

GTPase activator for the nuclear Ras-related regulatory protein Rap1, converting it to the putatively inactive GDP-bound state (according to Swiss-Prot); Regulation of small GTPase-mediated signal transduction.

Homology

The RAP1GAP gene is conserved in cow, mouse, rat, zebrafish, fruit fly, mosquito, and *C. elegans*.

Implicated in

Solid tumors

Disease

Papillary thyroid cancer, pancreatic cancer, prostate cancer, melanoma tumors

Oncogenesis

Rap1GAP, which acts as a GTPase activator for the nuclear Ras-related regulatory protein Rap1, was a specific negative regulator of Rap1, and the monomeric G protein Rap1 has been implicated in cancer tumorigenesis. It signals to pathways involved in cell adhesion, migration, and survival. Loss of Rap1GAP was discovered in papillary thyroid cancer, pancreatic cancer, prostate cancer, melanoma tumors, and their cell lines, all of them exhibited increased Rap1 activity, that activation of Rap1 promotes cell proliferation and migration potentiality through the mitogen-activated protein kinase pathway and integrin activation. As a putative tumor suppressor gene, Rap1GAP inhibits tumor growth but induces MMP2- and MMP9-mediated squamous cell carcinoma invasion and tumor progression, suggesting a role for this protein as a biomarker for early N-stage, aggressive squamous cell carcinomas.

Myelodysplastic syndrome (MDS)

Disease

The expression level of Rap1GAP in MDS patients significantly increased as compared with patients with non-malignant blood diseases or acute myeloid leukemia (AML). Among MDS patients, the expression level of Rap1GAP in MDS-refractory anemia (RA) was significantly higher than that in MDS-refractory anemia with excess of blasts (RAEB). On the other hand, inhibiting Rap1 activity by expression of Rap1GAP increased leukocyte transendothelial migration, providing physiological relevance to the hypothesis that Rap1 augments barrier function of inter-endothelial cell junctions, implying the relevance of Rap1GAP in the regulation of haematogenesis.

References

Wittchen ES, Worthylake RA, Kelly P, Casey PJ, Quilliam LA, Burrige K. Rap1 GTPase inhibits leukocyte transmigration by promoting endothelial barrier function. *J Biol Chem*. 2005 Mar 25;280(12):11675-82

Zhang L, Chenwei L, Mahmood R, van Golen K, Greenson J, Li G, D'Silva NJ, Li X, Burant CF, Logsdon CD, Simeone DM. Identification of a putative tumor suppressor gene Rap1GAP in pancreatic cancer. *Cancer Res*. 2006 Jan 15;66(2):898-906

Zhang Z, Mitra RS, Henson BS, Datta NS, McCauley LK, Kumar P, Lee JS, Carey TE, D'Silva NJ. Rap1GAP inhibits tumor growth in oropharyngeal squamous cell carcinoma. *Am J Pathol*. 2006 Feb;168(2):585-96

Mitra RS, Goto M, Lee JS, Maldonado D, Taylor JM, Pan Q, Carey TE, Bradford CR, Prince ME, Cordell KG, Kirkwood KL, D'Silva NJ. Rap1GAP promotes invasion via induction of matrix metalloproteinase 9 secretion, which is associated with poor survival in low N-stage squamous cell carcinoma. *Cancer Res*. 2008 May 15;68(10):3959-69

Qi X, Chen Z, Qian J, Cen J, Gu M. Expression of Rap1GAP in human myeloid disease following microarray selection. *Genet Mol Res*. 2008 Apr 29;7(2):379-87

Bailey CL, Kelly P, Casey PJ. Activation of Rap1 promotes prostate cancer metastasis. *Cancer Res*. 2009 Jun 15;69(12):4962-8

Ika SA, Qi XF, Chen ZX. Protein RAP1GAP in human myelodysplastic syndrome detected by flow cytometry and its clinical relevance. *Zhongguo Shi Yan Xue Ye Xue Za Zhi*. 2009 Jun;17(3):612-7

Nellore A, Paziana K, Ma C, Tsygankova OM, Wang Y, Puttaswamy K, Iqbal AU, Franks SR, Lv Y, Troxel AB, Feldman MD, Meinkoth JL, Brose MS. Loss of Rap1GAP in papillary thyroid cancer. *J Clin Endocrinol Metab*. 2009 Mar;94(3):1026-32

Zheng H, Gao L, Feng Y, Yuan L, Zhao H, Cornelius LA. Down-regulation of Rap1GAP via promoter hypermethylation promotes melanoma cell proliferation, survival, and migration. *Cancer Res*. 2009 Jan 15;69(2):449-57

This article should be referenced as such:

Chen Z, Shao X. RAP1GAP (RAP1 GTPase activating protein). *Atlas Genet Cytogenet Oncol Haematol*. 2010; 14(11):1034-1035.
