Atlas of Genetics and Cytogenetics in Oncology and Haematology

OPEN ACCESS JOURNAL AT INIST-CNRS

Gene Section

Mini Review

RHOC (ras homolog gene family, member C)

Ahmad Faried, Leri S Faried

Department of General Surgical Science (Surgery I), Graduate School of Medicine, Gunma University, Maebashi, Japan

Published in Atlas Database: June 2007

Online updated version: http://AtlasGeneticsOncology.org/Genes/RHOCID42110ch1p13.html
DOI: 10.4267/2042/38463

Identity

Hugo: RHOC
Other names: ARH9; ARHC; H9; MGC1448; MGC61427; RhoH9
Location: 1p13.1

DNA/RNA

Description

The RhoC gene contains 6 exons and 5 introns. It was predicted to span over approximately 6.3 kb of the genomic DNA with mRNA size approximately 1116 bp. This gene is related to a gene originally identified in the marine snail, Aplysia. After the original cloning of Rho gene in Aplysia californica, then several genes in mammal been identified and divided into several subfamily, among them is (RhoA, RhoB and RhoC isoforms). In 1993, human ARH9 (RhoC), was reexamined and showed that it was present in choromosome 1. Human cDNA of RhoC proteins were isolated from the complete H9Rho (clone 9) coding sequence. Other group isolated RhoC from adult retina library.

Transcription

Three alternative transcripts encoding the same protein have been identified for RhoC gene.

Protein

Description

The primary protein sequences of Rho-subfamily (RhoA, B and C) are about 85% identical, with most divergence close to the C-terminus. The sequence divergence among RhoA, B and C is found in the insert loop, a helix between amino acids 123 and 137. The RhoC consists of 193 amino acids corresponding to a molecular weight of 22 kDa. RhoC protein consists of GTPase binding domain in the N-terminal. In C-terminal consists of geranylgeranyl group and carboxyl methylation extension. RhoC contains the sequence motif of GTP-binding proteins, bind to GDP and GTP with high affinity and are involved in cycle between in-active, GDP-bound and active, GTP-bound states. RhoC displays about 30% amino acids identity with Ras proteins which mainly clustered in four highly homologues internal region corresponding to the GTP binding site.

Expression

The RhoC proteins are over-expressed in bladder carcinoma, breast carcinoma, and in the squamous cell carcinoma of the head and neck. At mRNA level, RhoC are over-expressed in adenocarcinoma of the ovary, pancreatic cancer and hepatocellular carcinoma.

Localisation

Mainly in the cytoplasm, there is a small fraction localized in the plasma membrane of the Rat-2 fibroblast cells and associated with undefined perinuclear structures.

Function

The Rho proteins are involved in multiple processes, such as organization of the cytoskeletal components, cell division or intracellular trafficking. Role of RhoC also been observed in limb development. The RhoC protein has been connected to cancer development. It is up-regulated in malignant pancreatic ductal carcinoma, inflammatory breast cancer tumors and highly metastatic melanoma. Ectopic over-expression of this gene increases the tumorigenic and metastasis properties of tumor progenitor cell. RhoC also induces the expression of angiogenic factors in human mammary epithelial cells, by facilitating the vascularization of tumors in which it is expressed.

Homology

At least there are five homologues of RhoC sequences with pair-wise similarity from 80-100% at the amino acids level. Among them in dog (Canis lupus familiaris), rat (Rattus norvergicus), mouse (Mus musculus), zebrafish (Danio rerio), and chicken (Gallus gallus).

Mutations

Germinal

Not found in Homo sapiens.

Somatic

Not found in Homo sapiens.

Implicated in

Morphogenesis

Note: The RhoC exhibits specific expression domain in regions undergoing major cell rearrangement process in the developing limb autopod, including the prechondrogeneic aggregates, the developing interphalangeal joints and tendons. Functional experiments indicate that RhoC is a regulator of mesenchymal cell shape and adhesiveness, acting as a modulator of digit morphogenesis and joint formation.

Malignancy

Disease

The RhoC reported to be over-expressed in many human cancers (see above).

Prognosis

The RhoC over-expression is a predictor of poor prognosis in malignancy.

Oncogenesis

The RhoC and RhoA are 94% identical, only 11 amino acids are different. RhoC plays a major role in cell locomotion compare with RhoA. Over-expression of RhoC is closely related with tumor cell invasion and metastasis.

References

Madaule P, Axel R. A novel ras-related gene family. Cell 1985;41:31-40.

Chardin P, Madaule P, Tavitian A. Coding sequence of human rho cDNAs clone 6 and clone 9. Nucl. Acids Res 1988;16:2717.

Adamson P, Paterson HF, Hall A. Intracellular localization of the P21rho proteins. J. Cell Biol 1992;119:617-627.

Morris SW, Valentine MB, Kirstein MN, Huebner K. Reassignment of the human ARH9 RAS-related gene to chromosome 1p13-p21. Genomics 1993;15:677-679.

Fagan KP, Oliveira L, Pittler SJ. Sequence of rho small GTP-binding protein cDNAs from human retina and identification of novel 5' end cloning artifacts. Exp. Eye Res 1994;59:235-237.

Ihara K, Muraguchi S, Kato M, Shimizu T, Shirakawa M, Kuroda S, Kaibuchi K, Hakoshima T. Crystal structure of human RhoA in a dominantly active form complexed with a GTP analogue. J. Biol. Chem 1998;273:9656-9666.

Suwa H, Ohshio G, Imamura T, Watanabe G, Arii S, Imamura M, Narumiya S, Hiai H, Fukumoto M. Overexpression of the rhoC gene correlates with progression of ductal adenocarcinoma of the pancreas. Br. J. Cancer 1998;77:147-152.

Clark EA, Golub TR, Lander ES, Hynes RO. Genomic analysis of metastasis reveals an essential role for RhoC. Nature 2000;406:532-535.

van Golen KL, Wu ZF, Qiao XT, Bao LW, Merajver SD. RhoC GTPase, a novel transforming oncogene for human mammary epithelial cells that partially recapitulates the inflammatory breast cancer phenotype. Cancer Res 2000;60:5832-5838.

van Golen KL, Wu ZF, Qiao XT, Bao L, Merajver SD. RhoC GTPase overexpression modulates induction of angiogenic factors in breast cells. Neoplasia 2000;2:418-425.

Michaelson D, Silletti J, Murphy G, D'Eustachio P, Rush M, Philips MR. Differential localization of Rho GTPases in live cells: regulation by hypervariable regions and RhoGDI binding. J. Cell Biol 2001;152:111-126.

Kleer CG, van Golen KL, Zhang Y, Wu ZF, Rubin MA, Merajver SD. Characterization of RhoC expression in benign and malignant breast disease: a potential new marker for small breast carcinomas with metastatic ability. Am. J. Pathol 2002;160:579-584.

Horiuchi A, Imai T, Wang C, Ohira S, Feng Y, Nikaido T, Konishi I. Up-regulation of small GTPases, RhoA and RhoC, is associated with tumor progression in ovarian carcinoma. Lab. Invest 2003;83:861-870.

Kamai T, Tsujii T, Arai K, Takagi K, Asami H, Ito Y, Oshima H. Significant association of Rho/ROCK pathway with invasion and metastasis of bladder cancer. Clin. Cancer Res 2003;9:2632-2641.

Wang L, Yang L, Luo Y, Zheng Y. A novel strategy for specifically down-regulating individual Rho GTPase activity in tumor cells. J. Biol. Chem 2003;278:44617-44625.

Etienne-Manneville S. Actin and microtubules in cell motility: which one is in control?. Traffic 2004;5:470-477.

Ikoma T, Takahashi T, Nagano S, Li YM, Ohno Y, Ando K, Fujiwara T, Fujiwara H, Kosai K. A definitive role of RhoC in metastasis of orthotopic lung cancer in mice. Clin. Cancer Res 2004;10:1192-1200.

Wang W, Yang LY, Huang GW, Lu WQ, Yang ZL, Yang JQ, Liu HL. Genomic analysis reveals RhoC as a potential marker in hepatocellular carcinoma with poor prognosis. Br. J. Cancer 2004;90:2349-2355.

Wheeler AP, Ridley AJ. Why three Rho proteins? RhoA, RhoB, RhoC, and cell motility. Exp. Cell Res 2004;301:43-49.

Jaffe AB, Hall A. Rho GTPases: biochemistry and biology. Annu. Rev. Cell Dev. Biol 2005;21:247-269.

Faried A, Faried LS, Kimura H, Nakajima M, Sohda M, Miyazaki T, Kato H, Usman N, Kuwano H. RhoA and RhoC proteins promote both cell proliferation and cell invasion of human oesophageal squamous cell carcinoma cell lines in vitro and in vivo. Eur. J. Cancer 2006;42:1455-1465.

Kleer CG, Teknos TN, Islam M, Marcus B, Lee JS, Pan Q, Merajver SD. RhoC GTPase expression as a potential marker of lymph node metastasis in squamous cell carcinomas of the head and neck. Clin. Cancer Res 2006;12:4485-4490.

Montero JA, Zuzarte-Luis V, Garcia-Martinez V, Hurle JM. Role of RhoC in digit morphogenesis during limb development. Dev. Biol 2007;303:325-335.

This article should be referenced as such:

Faried A, Faried LS. RHOC (ras homolog gene family, member C). Atlas Genet Cytogenet Oncol Haematol.2008;12(1):8-9.