Gene Section

RHOA (ras homolog gene family, member A)

Teresa Gomez del Pulgar, Juan Carlos Lacal

Instituto de Investigaciones Biomédicas, Translational Oncology Unit, CSIC-UAM- La Paz, Madrid, Spain

Published in Atlas Database: January 2007


DOI: 10.4267/2042/38415

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: RHOA
Other names: ARH12; ARHA; H12; RHO12; RHOH12
Location: 3p21.31

DNA/RNA

Description
This gene can be found on Chromosome 3 at location: 49,371,585-49,424,530.

Transcription
The DNA sequence contains 5 exons and the transcript length is of 1919 bps translated to a 193 residues protein.

Protein

Description
RhoA encodes a 21-kDa, 193 amino acids, small Rho GTPase; it displays potent oncogenic activity when overexpressed.

RhoA structure:
The N-terminal half of RhoA contains the majority of the amino acids involved in GTP binding and hydrolysis, together with the Switch 1 and 2 regions that change conformation between the GTP-bound and GDP-bound states. Several X-ray crystallographic structures of RhoA have been solved at high resolution. Amino acids essential for catalytic function are conserved in other Rho proteins, including Gly14, Thr19, Phe30, and Gln63, which are involved in binding, stabilization or regulation of GTP hydrolysis. RhoA protein is target for several bacterial toxins, which modify key conserved amino acids involved in their regulation. These include Clostridium botulinum exoenzyme C3 transferase, which modifies Asn41, and Toxin B, which acts on Thr37.

The C-terminus of RhoA is essential for correct localization of the protein. RhoA is post-translationally modified by prenylation of a conserved C-terminal cysteine followed by methylation and proteolytic removal of the last three amino acids. The prenyl group (geranylgeranyl) anchors the GTPase into membranes and this modification is essential for its stability, cell growth, transformation, and cytoskeletal organization.

Expression
RhoA protein is expressed in all tissues tested.

Localisation
RhoA is found in the cytoplasm or at the plasma membrane.

RhoA activity regulation:
RhoA has intrinsic GTPase activity and shuttle between an inactive GDP-bound state and active GDP-bound state. In vitro, the exchange of GDP to GTP occurs very slowly, and is catalyzed by guanine nucleotide exchange factors (GEFs), which exchange GDP for GTP. GTPase activating proteins (GAPs) catalyze hydrolysis of the gamma phosphate of GTP. There are over 80 GEFs and 70 GAPs for Rho GTPases, whose activity is tightly regulated and can be highly specific. RhoA can be sequestered in the cytoplasm by guanine nucleotide dissociation inhibitors (RhoGDIs). These remove the Rho protein from the membrane by binding to the prenyl group and prevent its interaction with downstream effectors.

RhoA effectors binding:
To date, at least 11 proteins have been identified which directly interact with RhoA (ROCK1, ROCK2, PRK1/2, PKN, Rhotekin, Rhophilin, kinectin, Citron Kinase, MBS, p76RBE, PKC epsilon and DB1 transcription factor). Some of these have been shown to contribute to specific responses downstream of RhoA.
Similarly to GEFs and GAPs, effectors bind to Rho both through the Switch 1 and 2 regions, but the amino acids involved in interaction with each target differ.

**Function**

RhoA regulates a diverse set of biological activities including actin organization, cell motility, cell polarity, gene transcription and cell-cycle progression.

**Role in actin organization:**

RhoA protein plays a central role in regulating cell shape, polarity and locomotion through their effects on actin polymerization, actomyosin contractility, cell adhesion, and microtubule dynamics. RhoA is believed to act primarily at the rear of migrating cells to promote detachment.

RhoA directly stimulates actin polymerization through activation of diaphanous-related forms (DRFs, also known as Dia proteins). These stimulate addition of actin monomers to the fast-growing end of actin filaments. DRFs act together with ROCKs to mediate Rho-induced stress fiber formation. ROCK-mediated phosphorylation of LIMK and consequent inhibition of cofilin also contributes to the increase in actin filaments in response to Rho. In addition, ROCKs induce actomyosin-based contractility and phosphorylate several proteins involved in regulating myosins and other actin-binding proteins. Actomyosin contractility is important in migrating cells for detachment of the rear. Microtubules are essential for determining cell polarity as well as for vesicular locomotion and intracellular transport. The concerted action of ROCK and Dia is essential for the regulation of cell polarity and organization of microtubules. ROCK phosphorylates Tau and MAP2, proteins that regulate microtubule stability.

RhoA plays a key role in regulating the integrity of cell-extracellular matrix and cell-cell adhesions, the latter including both adherens junctions and tight junctions. Loss of cell-cell junctions is required for the migration of epithelial cells and may be regulated reciprocally by ROCKs and DRFs.

**Role in cytokinesis:**

Cytokinesis requires actomyosin-based contraction. Inhibition of ROCK or citron kinase causes defects in cytokinesis resulting in multinucleate cells. Diaphanous-related forms (DRFs) are also implicated in this process, the DRF mDia1 localizes to the cleavage furrow during cytokinesis. DRFs could contribute to cytokinesis by stimulating local actin polymerization and/or by coordinating microtubules with actin filaments at the site of the contractile ring.

**Role in cell cycle regulation:**

RhoA plays a pivotal role in G1 cell cycle progression, primarily through regulation of both cyclin D1 expression, and the levels of the cyclin-dependent kinase inhibitors p21 and p27. Multiple pathways seem to link Rho proteins to the control of cyclin D1 levels. Many of these involve the activation of protein kinases, leading to the subsequent modulation of transcription factor activity. RhoA suppresses p21 levels in multiple normal and transformed cell lines. This effect appears to occur through a transcriptional mechanism but is independent of p53, a major transcriptional regulator of p21. RhoA plays an important role in determining the levels of p27 through a pathway involving its effector, the Rho-associated kinases.

**Role in development:**

RhoA protein is required for processes involving cell migration in development including: neurite outgrowth, dorsal closure, bone formation, and myogenesis. Rho-loss of function is embryonically lethal in mouse development by E7. This is attributed to failure in gastrulation and an inability of cells to migrate.

**Role in transcriptional control:**

The relationship between many of the cellular functions mediated by RhoA with transcriptional regulation has been described. RhoA modulates the activity of SRF, NF-kappaB, c/EBPb, Stat3, Stat5, FHL-2, PAX6, GATA-4, E2F, Estrogen Receptor alpha, Estrogen Receptor beta, CREB, and transcription factors that depend on the JNK and p38 MAP kinase pathways. Substrates to these kinases include c-Jun, ELK, PEA3, ATF2, MEF2A, Max and CHOP/2GADD153.

**Mutations**

**Note:** Several types of human cancers have been analyzed for RhoA mutations. Thus, breast, ovarian, renal, lung and colon specimens were surveyed for RhoA gene mutations and performed chromosomal analysis on 3p21. No mutations in RhoA were found, nor any correlation between RhoA mRNA expression and the presence or absence of 3p21 deletions.

**Implicated in**

**Breast carcinoma**

**Oncogenesis**

RhoA protein levels were significantly increased in breast cancer compared with the corresponding normal tissue. Of particular note, protein levels of RhoA were barely detectable in normal mammary tissue, but were highly expressed in all breast tumors tested. Interestingly, RhoA protein levels correlated with increasing breast tumor grade.

**Ovarian carcinoma**

**Oncogenesis**

RhoA mRNA is higher in ovarian carcinoma, especially of serous histological type, than in benign tumors. The expression of the protein is further upregulated in tumors of stages III/IV when compared to those of stages I/II. Analysis of matched pairs of primary and metastatic lesions showed that expression of both RhoA mRNA was significantly higher in
metastatic lesions of peritoneal dissemination than in the respective primary tumors.

**Testicular cancer**

**Oncogenesis**

Protein expression of RhoA and its two major downstream effectors ROCK-I and ROCK-II, was significantly higher in tumor tissue than in nontumor tissue from 57 patients with testicular germ cell tumors. The expression was greater in tumors of higher stages than lower stages, thus RhoA correlates with tumor stage and aggressiveness.

**Pelvic/ureteric cancer**

**Oncogenesis**

Both mRNA and protein level of RhoA are elevated in pelvic/ureteric cancer with an increase in lymph node metastasis. The expression levels of RhoA were related to poorly differentiated grade and muscle invasion and associated with a shorter disease-free and overall survival. These findings suggest that RhoA is involved in the invasion and metastasis of upper urinary tract cancer, indicating that RhoA may be a useful prognostic factor in this disease.

**Bladder cancer**

**Oncogenesis**

A similar deregulation of RhoA is observed in bladder cancer. In this sense, RhoA and ROCK protein levels are elevated in tumors, again with higher expression in less differentiated tumors and metastatic lymph nodes compared to normal bladder. Interestingly, the levels of expression of RhoA and ROCK correlated positively with one another suggesting that the GTPase and its effector synergize to promote tumor progression.

**Lung tumors**

**Oncogenesis**

Of the two major forms of lung cancer, small cell lung carcinoma (SCLC) and non-small cell lung carcinoma (NSCLC), the former has a greater metastatic potential. The expression and activation of RhoA is greater in SCLC than NSCLC cell lines. It has been observed that RhoA repress the expression of nitric oxide synthase-2 (NOS-2) in a lung cancer-derived cell line. Since NOS-2 activity is related to reduced proliferation, RhoA could be eliminating this antiproliferative signal in lung carcinogenesis. In addition, inhibition of RhoA by C3 exoenzyme or through ADP-ribosylation leads to an increase in cadherin-based adhesion and loss of motility of SCLC.

**Oesophageal squamous cell carcinoma**

**Oncogenesis**

There were significant correlations among RhoA overexpression and TNM clinical classification, lymphatic invasion, and blood-vessel invasion. The five-year survival rates for ESCC patients with RhoA overexpression were significantly lower than those in patients with RhoA under-expression. The expression of RhoA protein appeared to be correlated with tumour progression of ESCC. Patients with RhoA overexpression tended to have poor prognosis compared with patients with RhoA under-expression.

**Gastric cancer**

**Oncogenesis**

RhoA was found frequently overexpressed in gastric cancer tissues compared with normal tissues, suggesting that RhoA may play a critical role in the carcinogenesis of this type of cancer. The interference of RhoA expression and/or activity could significantly inhibit the proliferation and tumorigenicity of gastric cancer cells and enhance the chemosensitivity to therapeutic agents such as Adriamycin and 5-fluouracil.

**Hepatocellular carcinoma**

**Oncogenesis**

Invasiveness of hepatocellular carcinoma is facilitated by the Rho/Rho-kinase pathway and likely to be relevant to tumor progression. The Rho/Rho-kinase may be useful as a prognostic indicator and in the development of novel therapeutic strategies.

**Pancreatic tumor**

**Oncogenesis**

Although overexpression of RhoA has not been detected in any pancreatic tumor tissue to date, it might nevertheless also be involved in pancreatic tumors. Two 3-hydroxy 3methylgultaryl coenzyme A (HMG-CoA) reductase inhibitors, fluvastatin and lovastatin inhibit human pancreatic cancer cell invasion and metastasis in a Rho-dependent manner. These inhibitors prevent the synthesis of cholesterol precursors necessary for proper membrane translocation of Rho protein.

**Colorectal cancer**

**Oncogenesis**

A high proportion of colon cancers overexpress RhoA and several aspects of colon tumor biology have been related to Rho GTPases. Leptin receptor and leptin-induced migration of colonic epithelial cancer cells is dependent on RhoA, since inhibition of the activity of the GTPase through introduction of dominant negative mutants completely abolishes the invasive capacity of the tumor cells.

**References**


Genda T, Sakamoto M, Ichida T, Asakura H, Kojiro M, Narumiya S, Hirohashi S. Cell motility mediated by rho and Rho-associated protein kinase plays a critical role in...

This article should be referenced as such: