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Gene Section

Review

RND3 (Rho family GTPase 3)

Xia Hongwei, Zhang Yucheng, Bi Feng

The Laboratory of Signal Transduction and Molecular Targeting Therapy, State Key Laboratory of Biotherapy, West China Hospital, Sichuan University, Chengdu 610041, China (XH, ZY, BF)

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Identity

Other names: ARHE, Rho8, RhoE, memB

HGNC (Hugo): RND3

Location: 2q23.3

DNA/RNA

Description

According to Entrez-Gene, RND3 gene maps to NC_000002.11 in the region between 151324709 and 151344180. According to Spidey (mRNA to genomic sequence alignment tool, http://www.ncbi.nlm.nih.gov/spidey), RND3 has 6 exons, the sizes being 100, 190, 88, 110, 135, 2047.

Protein

Description

RND3 encodes a 26 kDa, 229 amino acids small GTPase protein that belongs to the Rho family of Ras GTPases superfamily. RND3 is a novel and unusual member of the Rho family because its activity is not controlled by two different reactions: the GDP/GTP exchange and the GTP-hydrolysis. So it is unable to hydrolyze GTP and is resistant towards GAP activity. They possess extended chains at both termini and four amino acids are responsible for RND3 GTPase deficiency: Ser32, Gln33, Ser79 and Ser81. And mutations of these codons in ras genes (Gly12, Gly13, Ala59 and Gln61) are responsible for Ras-mediated malignant transformation. The structure also implicated that it may also make the GTP-bound conformation of switch II stabe and could prevent conformational changes required during hydrolysis.

Expression

RND3 expression is highly regulated in response to multiple different stimulies and conditions.

At transcription, RND3 could be directly regulated by many transcriptional factors, including P53, HIF-1a, Foxd3, NF-KB, etc. RND3 mRNA and protein levels was up-regulated upon DNA damage-inducing stimuli including chemotherapeutic agents and ultraviolet (UV) irradiation. The response to genetoxic agents is mediated by p53, which binds specifically to the RND3 promoter and regulates RND3 expression while UV-induced RND3 up-regulation in keratinocytes does not depend on p53 status.

So there must be other DNA damage-induced transcription factors to stimulate RND3 transcription. For example, NF-kB could induce RND3 expression in prostate cancer cells. Hypoxia-inducible factor (HIF)-1 can increase RND3 protein levels, thereby promotes epithelial to mesenchymal transition in gastric cancer cells under hypoxic conditions. The induced RND3 expression represents a pivotal cellular adaptive response to hypoxia with implications in gastric cancer cell EMT and invasion. In addition, mutant B-Raf promotes migration and invasion through inducing RND3 expression in melanoma cells. FOXD3 was proved to be recruited to the RND3 promoter and downregulated RND3 expression at the mRNA and protein levels, thus downregulates migration and invasion in melanoma cells. The mTOR pathway is responsible for the increased expression of RND3 in subependymal giant cell astrocytomas and rare brain tumours where the mTOR inhibitors TSC1 or TSC2 are mutated. The TGF-b pathway is also involved in the RND3 expression since the TGF-b family member MIC-1/GDF15 could reduce the RND3 expression in prostate cancer cells.

At post-transcription, RND3 mRNA could also be a target of the miRNAs. Mir-200b directly

downregulated the expression of RND3 at the mRNA and protein levels, promoted expression of the downstream protein cyclin D1 and increased S-phase entry in HeLa cells. There is also study showing that RND3 mRNA may be a target of the miR-200c in breast cancer cells. MiR-17 targets RND3 tumor suppressor gene, promotes cell proliferation, tumor growth, cell cycle progression in colorectal carcinoma.

Localisation

Located in the membranes, Golgi.

Function

RND3 is an atypical member of the Rho family, and the study about this molecule is relatively fewer than other members of the Rho family. However the recent study shows that RND3 could regulate a diverse set of biological activities including actin organization, cell motility, cell-cycle progression, apoptosis and development.

Role in actin organization

Many studies on the functions of RND3 have been carried out in several cultured cell lines, most of these studies have shown that RND3 could regulate the actin cytoskeleton by inducing loss of stress fibres and cell rounding.

Previous studies have shown that RND3 interacts with p190 RhoGAP and might increase the intrinsic GAP activity of p190 RhoGAP for RhoA, thereby reducing RhoA-GTP levels. Recent reports have shown that a KERRA (Lys-Glu-Arg-Arg-Ala) sequence in their N-terminus of RND3 could mediate the lipid raft targeting of p190 RhoGAP correlated with its activation. RND3 could also negatively regulates Syx (a RhoA-GEF) through interacting with Syx Raf1-like ubiquitin-related domain thus act as an antagonists of RhoA signaling.

RhoA directly stimulates stress fibres through activation of the serine/threonine kinases ROCK1 and ROCK2. RND3 could interact with the amino-terminal region of ROCK1 comprising the kinase domain, so RND3 competited with other ROCK1 substrates, such as myosin light chain phosphatase, and hence prevent stress fibre formation.

Role in cell cycle regulation

Many studies have been indicated that RND3 could inhibit cell proliferation and these data show that RND3 is able to block cell-cycle progression at different phases.

Most studies about cell-cycle shown that RND3 could block cell-cycle progression at the G1 phase. The mechanism may be that RND3 could decrease the level of cyclin D1, reduce Rb phosphorylation and transcription of E2F-regulated genes. RND3 blocks the phosphorylation of the translational repressor 4E-BP1

in response to extracellular stimuli and also inhibits the expression and transcriptional activity of the eIF4E target c-Myc. Recent studies show that elevation of RND3 expression markedly increased the expression level of PTEN and p27 and decreased pAkt level, thus inhibit cell-cycle progression.

RND3 could also block cell-cycle progression at the G2/M phase. The study in a prostate cancer cell line shows that forced RND3 overexpression inhibits the expression of CDC2 and cyclin B1 which are essential for G2/M transition and induction of G2/M arrest.

Role in cell apoptosis and survival

The fuction of RND3 is complex, RND3 can modulate cell survival and apoptosis. RND3 can induce apoptosis in prostate cancer, esophageal squamous cell carcinoma and glioblastoma cell lines. However, in some cancer cell lines, high levels of RND3 can decrease apoptosis and ShRNA mediated RND3 depletion resulted in an increase in apoptosis in response to genotoxic agents or UVB. RND3 could increase survival in osteosarcoma cells through down-regulate the activity of ROCK1 which itself can mediate membrane blebbing and apoptosis in these cells. RND3 may promote the multidrug resistance phenotype of gastric cancer cells by decreasing the expression of pro-apoptotic protein Bax at post-transcriptional level.

Role in development

RND3 plays an important role in the normal development, RND3 null mice (RND3 gt/gt) show an abnormal body position with profound motor impairment and impaired performance in most neurobehavioral tests, they are smaller at birth, display growth retardation and early postnatal death. There is a delay of neuromuscular maturation, a reduction in the number of spinal motor neurons, a decrease in the number and the total length of the neurites in the RND3 gt/gt mice.

Over-expression of RND3 induces neurite-like formation through inhibition of the RhoA/ROCK-I signalling and also involves in NGF-induced neurite extension.

Implicated in

Lung tumors

Oncogenesis

RND3 expression was dramatically increased in the cytoplasm of lung cancer cells compared with undetectable expression of RND3 in the adjacent nontumoral cells. The cancer-related survival of RND3-negative patients are longer than that of RND3-positive ones. RND3 overexpression may serve as an independent marker for cancer-related survival in patients with non-small cell lung cancer. Overexpression of RND3 was also significantly associated with the patients' smoking history and DNA copy number changes.

Prostate cancer

Oncogenesis

RND3 mRNA and protein expression were significantly reduced in malignant tissue compared to

benign samples. Forced RND3 overexpression in a prostate cancer cell line inhibits the expression of CDC2 and cyclin B1, which induce G2/M arrest, and also increases apoptotic cell death. Genetic profiling of human prostate cancer cell lines shows that RND3 may serve as a potential new molecular marker for assessing the metastatic potential of PCa.

Mammary epithelial tumor

Oncogenesis

The expression level of RND3 in cancerous tissues was decreased or absent compared with adjacent normal tissues and RND3 could also serve as a negative marker in the development and progression of breast carcinoma. Exogenously expressed RND3/RND3 induces the formation of highly sealed tight junctions, co-localizes with actin at the cell periphery and induces beta-catenin and ZO-1 to sites of cell-cell contact in mammary epithelial tumor cells.

Human glioblastoma

Oncogenesis

Overexpression of RND3 disrupts actin cytoskeleton organization, inhibits cell proliferation and induces apoptosis in U87 glioblastoma cell line. RND3 reduces Rb phosphorylation, cyclin D1 expression and also inhibits ERK activation following serum stimulation of quiescent U87 cells.

Esophageal squamous cell carcinoma

Oncogenesis

The mRNA and protein expression levels of RND3 was significantly downregulated in ESCC (esophageal squamous cell carcinoma) tissues and cell lines, RND3 expression was tightly correlated with differentiation degree, clinical staging, and lymph node metastasis of the patients with ESCC, but there is no significant association between RND3 expression and gender or age of the patients with ESCC. Foced downregulation of RND3 expression in ESCC cells promoted cell proliferation, cell cycle progression, as well as cell invasion in vitro, and inhibited cell apoptosis, while upregulation of RND3 expression in ESCC cells inhibited cell proliferation, arrested cell cycle at G0/G1 phase, reduced cell invasion, and promoted cell apoptosis. RND3 may play an important role in the development and progression of ESCC.

Melanoma

Oncogenesis

Many studies have revealed that RND3 overexpressed in melanoma cells. B-Raf-mediated up-regulation of RND3 appears to participate in the promoting melanoma cell invasion by reorganizating the actin cytoskeleton and focal adhesions. Upregulation of FOXD3 expression inhibits the migration, invasion, and spheroid outgrowth of mutant B-RAF melanoma cells through downregulating RND3 expression at the transcriptional level.

Mesenchymal tumor

Oncogenesis

Reduced expression of RND3 increases invasiveness and metastatic potential in mesenchymal tumor cells while ectopic RND3 expression reduced their invasive ability in vitro and their metastatic potential in vivo.

Pancreatic cancer

Oncogenesis

A pancreatic cancer-specific expression profiling shows that RND3 is overexpressed in pancreatic cancer cells.

Liver cancer

Oncogenesis

Hepatocellular carcinoma (HCC) is the most common type of liver cancer. According to previous study, RND3 was down-regulated in HCC cell lines, as compared to nontumor liver cells. What's more, the patients with low expression of RND3 had a shorter survival than those with high expression. Therefore, RND3 expression could act as a significant prognostic predictor for HCC patients. The SiRNA-mediated down-regulation of Rnd3 expression induced a loss of E-cadherin and epithelial-mesenchymal transition through the up-regulation of the zinc finger E-box binding homeobox protein, ZEB2, and the down-regulation of miR-200b and miR-200c.

Gastric cancer

Oncogenesis

RND3 expression is down-regulated in gastric cancer cells and its expression is regulated by histone deacetylation, but not DNA methylation at the epigenetic levels in gastric cancer cells. However, RND3 expression is up-regulated in gastric cancer cells under hypoxic conditions. And HIF-1a could up-regulate RND3 expression through binding a hypoxia-responsive element (HRE) on the RND3 promoter at the transcriptional level. Besides, RND3 is overexpressed in the SGC7901 cell line and enhanced the resistance of SGC7901 cells to several kinds of antitumor drugs by decreasing the expression of Bax at post-transcriptional level.

Colorectal cancer

Oncogenesis

RND3 is downregulated in colorectal carcinoma (CRC) and RND3 expression was significantly lower in CRC tissues than in normal tissues and adenomas. Forced expression of RND3 can decrease the size of colorectal tumor and reduce the CD44 expression and further study shows that RND3 could inhibite the transcriptional activity of cd44 promoter. MiR-17 also plays an important role in CRC carcinogenesis by targeting RND3, thus promotes cell proliferation, tumour growth and cell cycle progression. However, recent study show RND3 could also promote invasion and metastasis in human colorectal cancer and it could

also serve as an independent prognostic marker in addition to the tumor, node, metastasis staging system. So the function of RND3 is complex.

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