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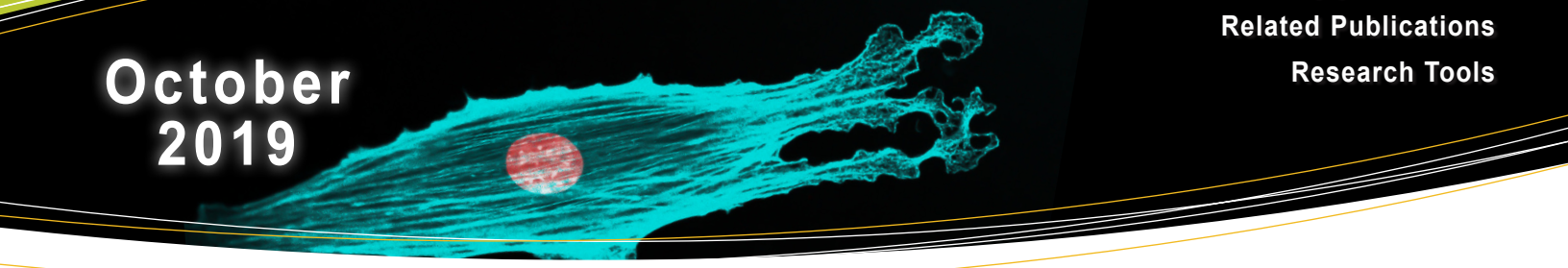

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RhoB GTPase: Tumor Promoter or Suppressor?

RhoB is a Rho-family GTPase that regulates essential physiological processes such as cell division, morphology, motility, adhesion, and intracellular transport, primarily through dynamic remodeling of the actin cytoskeleton, and whose expression and/or activity is pathologically dysfunctional in human diseases such as cancer and neurodegenerative diseases[1-3]. Due to its unique C-terminal region and distinct post-translational modifications there, RhoB is localized not only to the plasma membrane (like other Rho GTPases), but also to endosomes, multivesicular bodies, and even the nucleus[1,3] (Fig. 1). Like other Rho-family GTPases, RhoB functions as a binary switch in signaling cascades, cycling between a GDP-bound, inactive state and a GTP-bound, active state. The GTP/GDP cycling is controlled by guanine nucleotide exchange factors (GEFs; activation by exchanging GDP for GTP) and GTPase-activating proteins (GAPs; inactivation by GTP hydrolysis)[1-3].

RhoB expression and/or activity is regulated by a variety of physiological stimuli. Normally expressed at low levels under steady state conditions, RhoB expression and/or activity is rapidly up-regulated by hypoxia, growth factors, inflammatory cytokines, and stress stimuli including UV radiation[1,3-8] (Fig. 1). Upon activation, RhoB regulates cellular responses to UV-induced DNA damage, apoptosis, cell cycle progression, and cell migration (and invasion in the case of cancer cells)[1,3]. RhoB's distinctive subcellular localization to membrane vesicles enables RhoB-mediated regulation of intracellular transport. Endosome-localized RhoB regulates the trafficking (and thereby function) of receptor tyrosine kinase and cytokine receptor-mediated signaling cascades (e.g., EGFR, CXCR2, TNFR) and the activities of kinases such as Src and Akt[9-13] (Fig. 1). As a result, RhoB is able to regulate a wide range of essential signaling cascades involved in cellular development, proliferation, survival, and apoptosis – all pathways important in human physiology and disease[1,3].

RhoB expression and/or activity have a paradoxical relationship with tumorigenesis, as RhoB has been proposed to be both a tumor suppressor and tumor promoter, depending on the tumor microenvironment (i.e., context-dependent, cell-type specific, and even tumor stage-dependent)[1,3]. Initial recognition of RhoB's role in tumorigenesis was its requirement in Ras-mediated fibroblast transformation[14]. Recent studies also support a positive role for RhoB in tumorigenesis. In renal proximal tubular cells, RhoB knockdown correlates with a significant increase in apoptosis[15]. Similarly, knockdown of RhoB induces cell-cycle arrest and apoptosis and impairs tumorigenic potential in multiple glioblastoma cell lines[16]. Additional studies report elevated RhoB expression and/or activity in breast tumors vs normal tissue[17] and T-cell acute lymphoblastic leukaemia vs normal T-cells[18]. Furthermore, elevated RhoB in the primary tumor is predictive of a poor response to EGFR-RTK inhibitor treatment in lung cancer patients[19]. Increases in RhoB expression/activity also reduce survival in lung adenocarcinomas[20], impair the efficacy of chemoradiotherapy while enhancing metastatic potential in lung cancer cells[20], and seemingly protect certain cancer cell lines from radiation-induced apoptosis and mitotic cell death[21-23]. These findings led to the hypothesis that RhoB is important in developing and maintaining a malignant phenotype for at least certain cancers[3]. Conversely, there is a rich literature describing RhoB's ability to function as a tumor suppressor[3]. For instance, *in vitro* and *in vivo* models of cancer demonstrate that miRNA-mediated inhibition of RhoB mRNA expression correlates with increased cancer cell activity and/or tumorigenesis. miR-21-mediated inhibition of RhoB mRNA results in increased colorectal cancer cell proliferation, migration, and invasion, while miR-19a-mediated inhibition triggers pancreatic cancer *in vitro* and

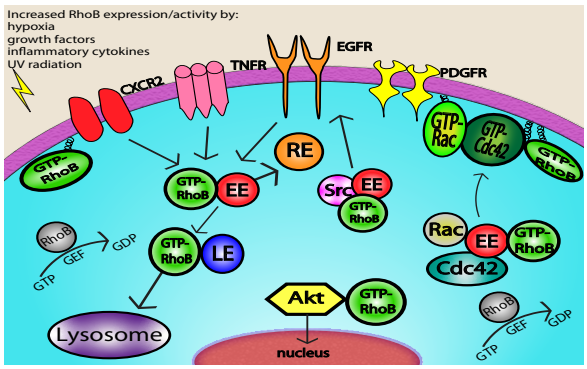

Figure 1. RhoB activation, localization, and roles in intracellular trafficking. Active (GTP-bound) RhoB localized to endosomes functionally regulates multiple growth factor and cytokine receptors (e.g., EGFR, CXCR2, TNFR), kinases (e.g., Src and Akt), and other GTPases (e.g, Rac and Cdc42) through various intracellular transport and recycling pathways. GTP-RhoB also localizes to the plasma membrane and has also been reported in the nucleus. EGFR, epidermal growth factor receptor; TNFR, tumor necrosis factor receptor; PDGFR, platelet-derived growth factor receptor; EE, early endosome; LE, late endosome; RE, recycling endosome. See text for further details and abbreviations.

GTPase Activation Kit PRODUCTS

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in vivo[1,3,24,25]. Additionally, RhoB is necessary for an apoptotic response to DNA damage or taxol treatment in transformed fibroblasts[26], and RhoB inhibits cancer cell migration, invasion, metastasis, and tumorigenesis in *in vitro* and *in vivo* oncogenic models in a cell-type and context-dependent manner[1,3,27,28]. In total, many studies report an inverse correlation between RhoB expression/activity and tumor progression in multiple types of cancers[1,3]. RhoB's opposing roles in tumorigenesis are likely determined by the type of cancer and tumor stage (e.g., initiation vs progression). The dependency on context (i.e., tumor microenvironment) both elucidates and complicates the relationship between cancers and RhoB and its potential as a therapeutic target[1,3]. These diverse and seemingly conflicting data also reinforce the need to think in terms of maintaining/regulating homeostasis in RhoB activity rather than in terms of inhibiting or activating RhoB activity[1,3].

Summary

Despite sharing significant amino acid sequence identity with RhoA and RhoC GTPases, RhoB exerts unique regulatory control over a wide range of cellular responses through many different signaling cascades, including control of the trafficking of other Rho-family GTPases such as Cdc42 and Rac, which themselves regulate cell migration[1,3] (Fig. 1). Importantly, RhoB's functions in tumorigenesis cannot be predicted from how RhoA and RhoC function. Thus, understanding the different conditions and contexts under which RhoB expression/activity is altered and the relationship to tumor progression or suppression is of paramount importance[3]. Deciphering these unknowns could offer significant therapeutic potential in the treatment of cancer, vascular, and inflammatory diseases[1,3]. To assist researchers, Cytoskeleton provides Ras and Rho-family GTPase activation assay kits, purified cytoskeletal proteins, cytoskeletal antibodies, live cell imaging reagents for cytoskeletal proteins, and Signal-Seeker kits to measure endogenous levels of post-translational modifications in cells and tissues.

Actin Biochem Kits

Product	Assays	Cat. #
Actin Binding Protein Spin-Down Assay Biochem Kit Rabbit skeletal muscle actin	30-100	BK001
Actin Polymerization Biochem Kit (fluorescence format) Measure actin polymerization *in vitro*, contains rabbit skeletal muscle actin.	30-100	BK003
Actin Binding Protein Spin-Down Assay Biochem Kit Human platelet actin	30-100	BK013
G-Actin/F-actin In Vivo Assay Biochem Kit Measure the distribution of monomer and polymer actin	30-100	BK037

Acti-Stain™ Phalloidins

Product	Amount	Cat #
Acti-stain 488™ phalloidin	300 Slides	PHDG1-A
Acti-stain 555™ phalloidin	300 Slides	PHDH1-A
Acti-stain 670™ phalloidin	300 Slides	PHDN1-A
Rhodamine Phalloidin	1 x 500 µl	PHDR1

Live Cell Imaging Products

Product	Ex / Em	Amount	Cat #
SiR-Actin™ Kit Includes SiR-Actin and Verapamil	630 / 680 nm	50 nmol	CY-SC001
SiR-Tubulin™ Kit Includes SiR-Tubulin, and Verapamil	630 / 680 nm	50 nmol	CY-SC002
SIR-DNA™ Kit Includes Verapamil	630 / 680 nm	50 nmol	CY-SC007
Flipper-TR™ Kit For fluorescence cell membrane microscopy	480 / 600 nm	50 nmol	CY-SC020

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G-LISA Activation Assay Kits

Product	Assays	Cat. #
RhoA G-LISA™ Activation Assay (Luminescence format)	96	BK121
RhoA G-LISA™ Activation Assay Kit (Colorimetric format)	96	BK124
Rac1,2,3 G-LISA™ Activation Assay (Colorimetric format)	96	BK125
Rac1 G-LISA™ Activation Assay (Luminescence format)	96	BK126
Rac1 G-LISA™ Activation Assay Kit (Colorimetric Based)	96	BK128
Ras G-LISA™ Activation Assay Kit (Colorimetric Based)	96	BK131
Total RhoA ELISA	96	BK150