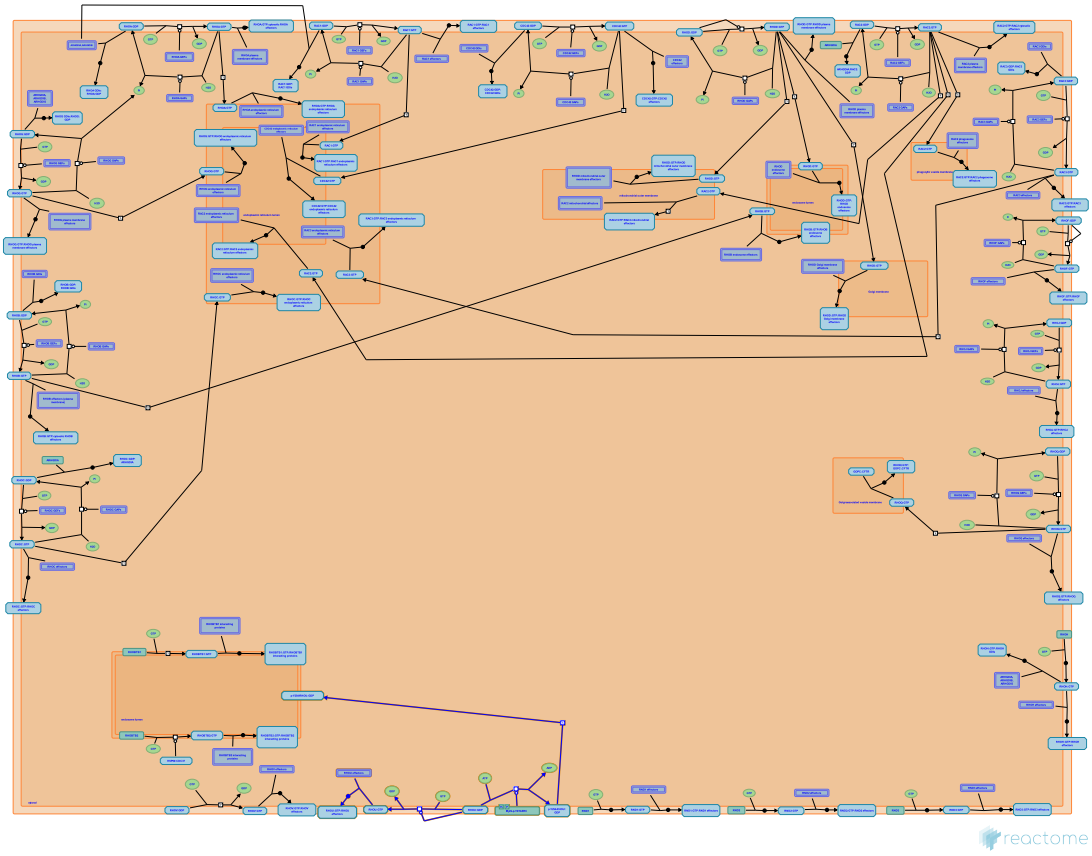
RHOU GTPase cycle



Fort, P., Orlic-Milacic, M., Shepelev, MV.

European Bioinformatics Institute, New York University Langone Medical Center, Ontario Institute for Cancer Research, Oregon Health and Science University.

This is just an excerpt of a full-length report for this pathway. To access the complete report, please download it at the Reactome Textbook.

23/04/2024

Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.
The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

Literature references

Fabregat, A., Sidiropoulos, K., Viteri, G., Forner, O., Marin-Garcia, P., Arnau, V. et al. (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC bioinformatics, 18*, 142. ↗

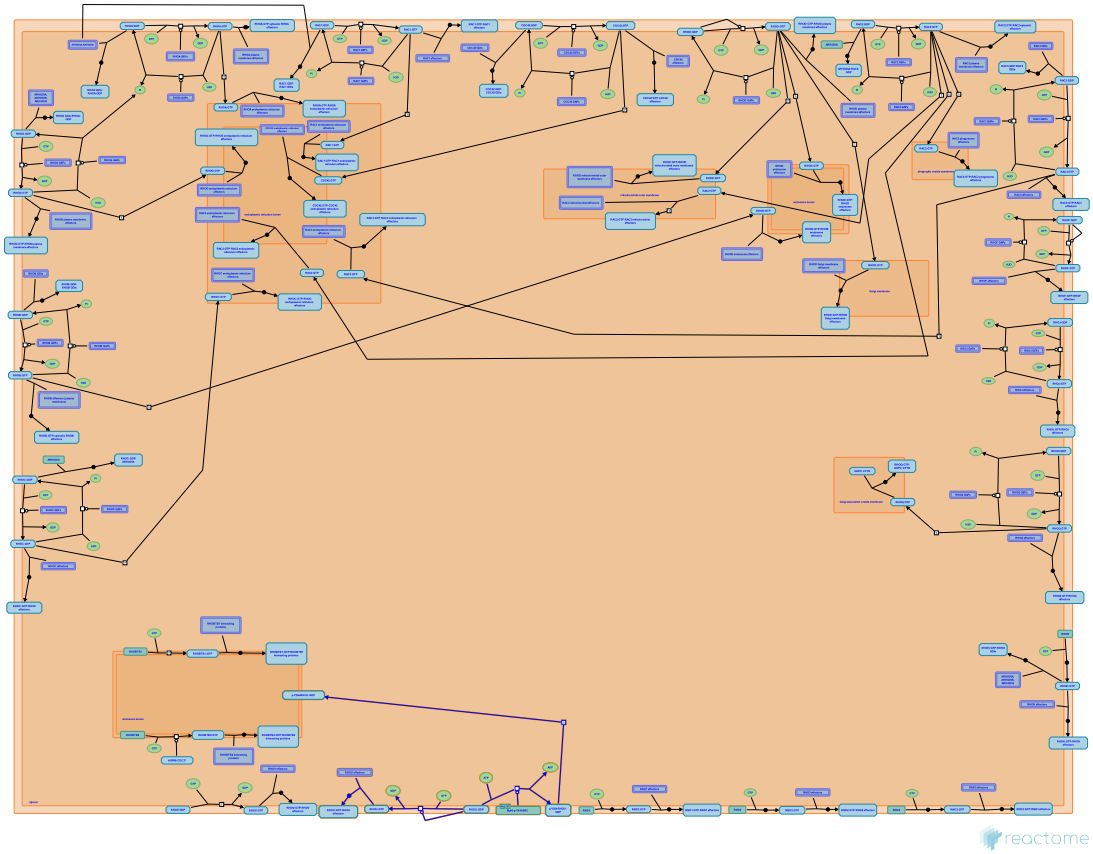
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

RHOU GTPase cycle ↗

Stable identifier: R-HSA-9013420



RHO GTPase RHOU (Wrch-1) possesses a high intrinsic guanine nucleotide exchange activity and is constitutively present in the active GTP-bound state in the absence of guanine nucleotide exchange factors (GEFs) (Shutes et al. 2004, Saras et al. 2004). RHOU does not possess a GTPase activity (Saras et al. 2004). RHOU has been reported to interact with some GTPase activator proteins (GAPs) (Bagci et al. 2020), which may serve as effectors that enable cross-talk with other RHO GTPases. RHOU was shown to regulate cytoskeletal dynamics, cell migration and adhesion. RHOU is expressed during embryonic development and regulates cardiac (Dickover et al. 2014) and intestinal (Slaymi et al. 2019) development. RHOU activates JNK and AKT signaling during cell migration (Chuang et al. 2007).
For review, please refer to Faure and Fort 2015, and Hodge and Ridley 2020.

Literature references

Fort, P., Faure, S. (2015). Atypical RhoV and RhoU GTPases control development of the neural crest. *Small GTPases, 6*, 174-7. ↗

Fort, P., Raynaud, P., Roux, P., Cres, G., Vignal, E., Blangy, A. et al. (2019). The atypical RhoU/Wrch1 Rho GTPase controls cell proliferation and apoptosis in the gut epithelium. *Biol Cell, 111*, 121-141. ↗

Valster, A., Chuang, YY., Coniglio, SJ., Symons, M., Backer, JM. (2007). The atypical Rho family GTPase Wrch-1 regulates focal adhesion formation and cell migration. *J Cell Sci, 120*, 1927-34. ↗

Ridley, AJ., Hodge, RG. (2020). Regulation and functions of RhoU and RhoV. *Small GTPases, 11*, 8-15. ↗

Der, CJ., Shutes, A., Cox, AD., Berzat, AC. (2004). Atypical mechanism of regulation of the Wrch-1 Rho family small GTPase. *Curr. Biol., 14*, 2052-6. ↗

Editions

2020-07-14	Authored	Orlic-Milacic, M.
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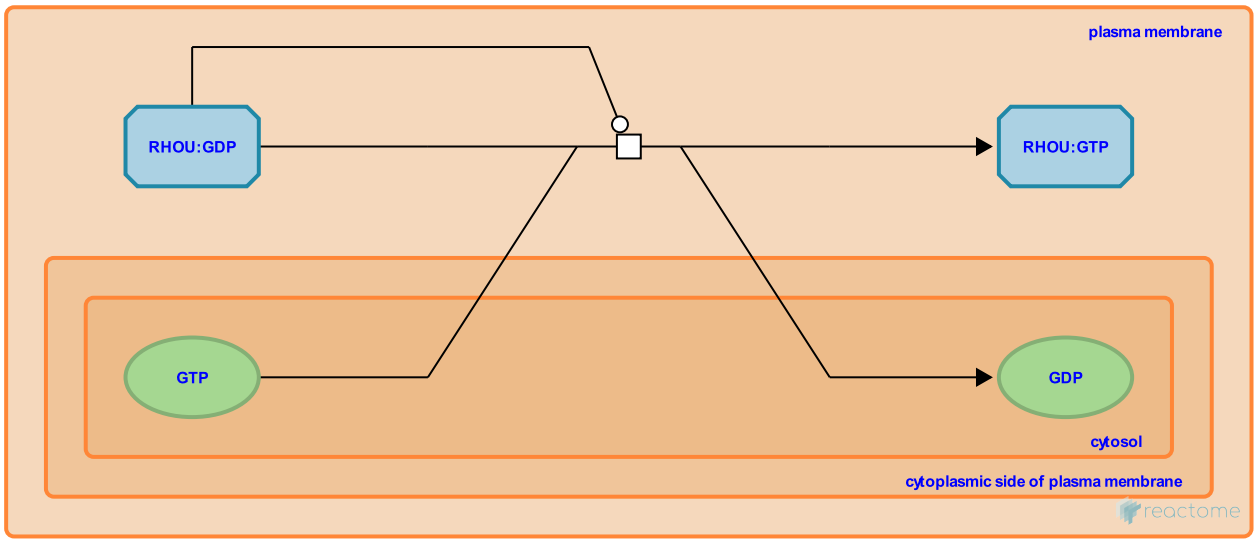
RHOU auto-activates ↗

Location: RHOU GTPase cycle

Stable identifier: R-HSA-9018768

Type: transition

Compartments: plasma membrane, cytosol



RHOU is an atypical RHO GTPase with a high intrinsic guanine nucleotide exchange activity. Guanine nucleotide exchange factors (GEFs) are not needed for RHOU activation (Shutes et al. 2004, Saras et al. 2004). While some GTPase activator proteins (GAPs) have been reported to interact with RHOU (Bagci et al. 2020), they have not been shown to act on RHOU. Instead, GAPs may serve as RHOU effectors that enable its cross talk with other RHO GTPases (reviewed in Hodge and Ridley 2020). RHOU was shown to possess GTPase activity (Shutes et al. 2004), but the functional importance of GTP hydrolysis in the context of high intrinsic GEF activity and no known GAPs has not been elucidated.

Followed by: RHOU binds effectors at the plasma membrane

Literature references

Wollberg, P., Saras, J., Aspenström, P. (2004). Wrch1 is a GTPase-deficient Cdc42-like protein with unusual binding characteristics and cellular effects. *Exp. Cell Res., 299*, 356-69. ↗

Der, CJ., Shutes, A., Cox, AD., Berzat, AC. (2004). Atypical mechanism of regulation of the Wrch-1 Rho family small GTPase. *Curr. Biol., 14*, 2052-6. ↗

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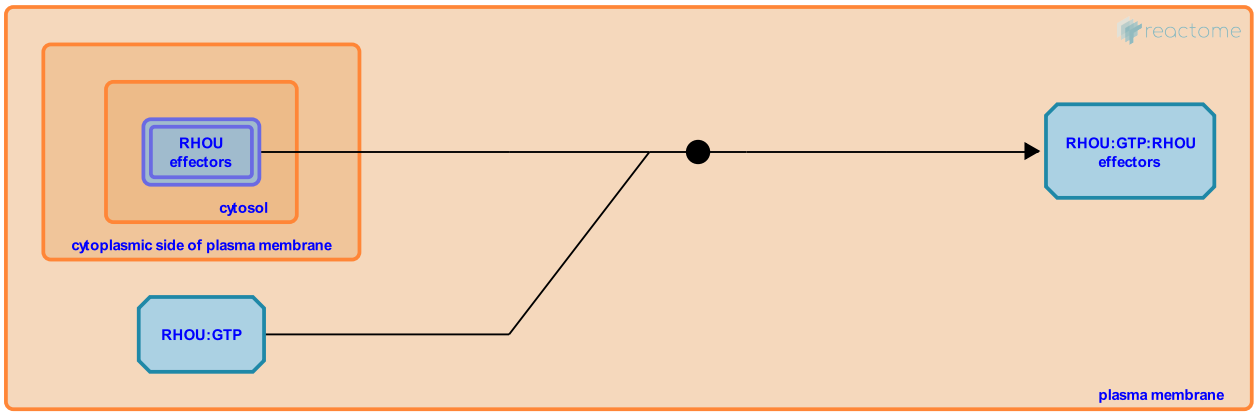
RHOU binds effectors at the plasma membrane ↗

Location: RHOU GTPase cycle

Stable identifier: R-HSA-9018766

Type: binding

Compartments: plasma membrane, cytosol



In its active GTP bound form, RHOU binds the following effectors:
ARHGAP30 (Naji et al. 2011; protein with GAP activity)
ARHGAP31 (Naji et al. 2011; protein with GAP activity)
GRB2 (Zhang et al. 2011; Bagci et al. 2020: weak binding)
ITSN2 (Gubar et al. 2020)
NCK2 (Saras et al. 2004; Bagci et al. 2020)
PAK1 (Tao et al. 2001; Shutes et al. 2004; Saras et al. 2004; Bagci et al. 2020)
PAK4 (Dart et al. 2015)
PAR6 (Brady et al. 2009)
PIK3R1 (Chuang et al. 2007; Bagci et al. 2020; protein with GAP activity)
PTK2B (Ruusala and Aspenström 2008)

The following candidate RHOU effectors were identified in the high throughput screen by Bagci et al. 2020:
ARHGEF6 (Bagci et al. 2020)
ARHGEF7 (Bagci et al. 2020)
CDC42 (Bagci et al. 2020)
CLTC (Bagci et al. 2020)
DEPDC1B (Bagci et al. 2020; protein with GAP activity)
DLG5 (Bagci et al. 2020)
DST (Bagci et al. 2020)
EPHA2 (Bagci et al. 2020)
GIT1 (Bagci et al. 2020)
GIT2 (Bagci et al. 2020)
HGS (Bagci et al. 2020)
IQGAP1 (Bagci et al. 2020)
MYO6 (Bagci et al. 2020)
NCK1 (Bagci et al. 2020)
PAK2 (Bagci et al. 2020)
PAK3 (Bagci et al. 2020)
PIK3R2 (Bagci et al. 2020; protein with GAP activity)
PEAK1 (Bagci et al. 2020)
SPTAN1 (Bagci et al. 2020)
SPTBN1 (Bagci et al. 2020)
SRGAP2 (Bagci et al. 2020; protein with GAP activity)
STAM (Bagci et al. 2020)
STAM2 (Bagci et al. 2020)
TXNL1 (Bagci et al. 2020)
USP9X (Bagci et al. 2020)
VANGL1 (Bagci et al. 2020)

WDR6 (Bagci et al. 2020)
WWP2 (Bagci et al. 2020)

RHOU does not bind WASL, a component of the WIP WASP complex (Bagci et al. 2020) and also does not bind:
CCP110 (Bagci et al. 2020)
CEP97 (Bagci et al. 2020)
MAP3K21 (Bagci et al. 2020)
MYH11 (Bagci et al. 2020)
MYL12B (Bagci et al. 2020)
SH3RF1 (Bagci et al. 2020)
TPM3 (Bagci et al. 2020)
TPM4 (Bagci et al. 2020)
ZNF512B (Bagci et al. 2020)

Preceded by: RHOU auto-activates

Literature references

Fanning, AS., Alan, JK., Cox, AD., Madigan, JP., Brady, DC. (2009). The transforming Rho family GTPase Wrch-1 disrupts epithelial cell tight junctions and epithelial morphogenesis. *Mol Cell Biol, 29*, 1035-49. ↗

Gryaznova, T., Croisé, P., Gubar, O., Gasman, S., Rynditch, A., Ory, S. et al. (2020). The atypical Rho GTPase RhoU interacts with intersectin-2 to regulate endosomal recycling pathways. *J Cell Sci, 133*. ↗

Valster, A., Chuang, YY., Coniglio, SJ., Symons, M., Backer, JM. (2007). The atypical Rho family GTPase Wrch-1 regulates focal adhesion formation and cell migration. *J Cell Sci, 120*, 1927-34. ↗

Billadeau, DD., Zhang, JS., Koenig, A., Young, C. (2011). GRB2 couples RhoU to epidermal growth factor receptor signaling and cell migration. *Mol Biol Cell, 22*, 2119-30. ↗

Brown, JP., Box, GM., Pinder, SE., Court, W., Wells, CM., Gale, ME. et al. (2015). PAK4 promotes kinase-independent stabilization of RhoU to modulate cell adhesion. *J. Cell Biol., 211*, 863-79. ↗

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SRC phosphorylates RHOU ↗

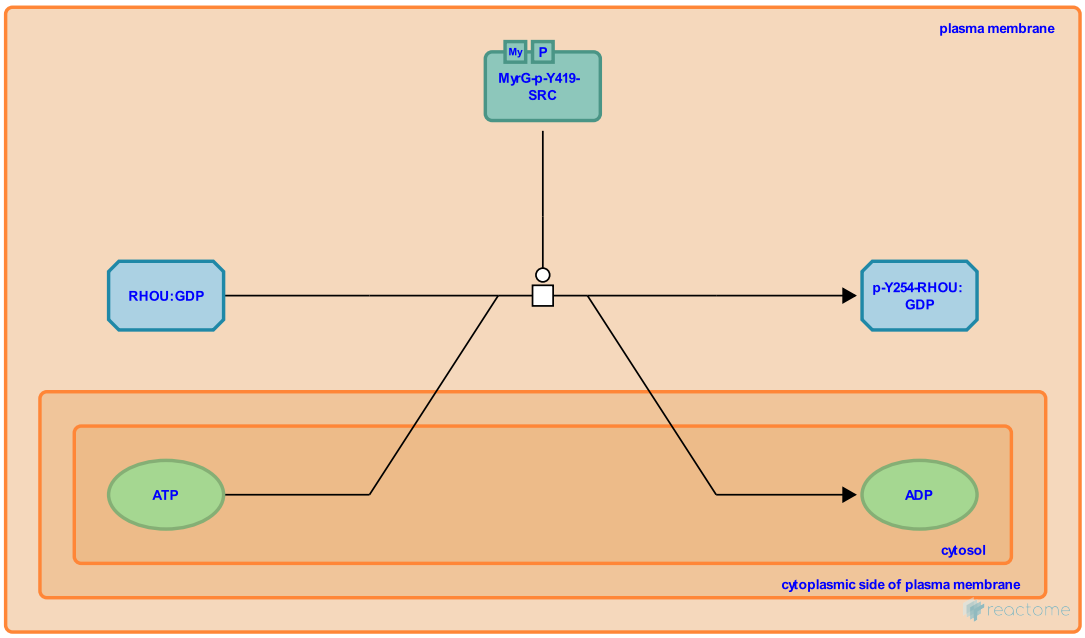
Location: RHOU GTPase cycle

Stable identifier: R-HSA-9726848

Type: transition

Compartments: plasma membrane

Inferred from: Src phosphorylates RHOU (Homo sapiens)



Based on studies conducted using human RHOU (Wrch-1) and mouse Src, SRC phosphorylates RHOU at the tyrosine residue Y254, located at the C-terminus of RHOU (Alan et al. 2010).

Followed by: Phosphorylated RHOU translocates to the endosome membrane

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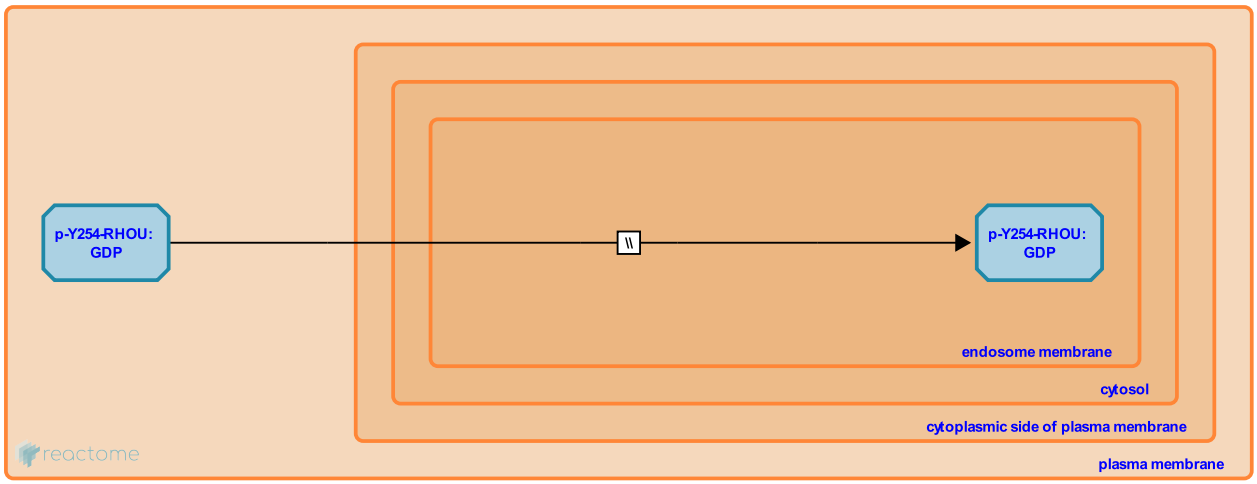
Phosphorylated RHOU translocates to the endosome membrane ↗

Location: RHOU GTPase cycle

Stable identifier: R-HSA-9726862

Type: omitted

Compartments: endosome membrane, plasma membrane



RHOU phosphorylated at tyrosine residue Y254 by SRC translocates from the plasma membrane to the endosome membrane where it is found in an inactive, GDP-bound state (Alan et al. 2010).

Preceded by: SRC phosphorylates RHOU

Literature references

Graves, LM., Alan, JK., Cox, AD., Berzat, AC., Dewar, BJ. (2010). Regulation of the Rho family small GTPase Wrch-1/RhoU by C-terminal tyrosine phosphorylation requires Src. *Mol Cell Biol, 30*, 4324-38. ↗

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Table of Contents