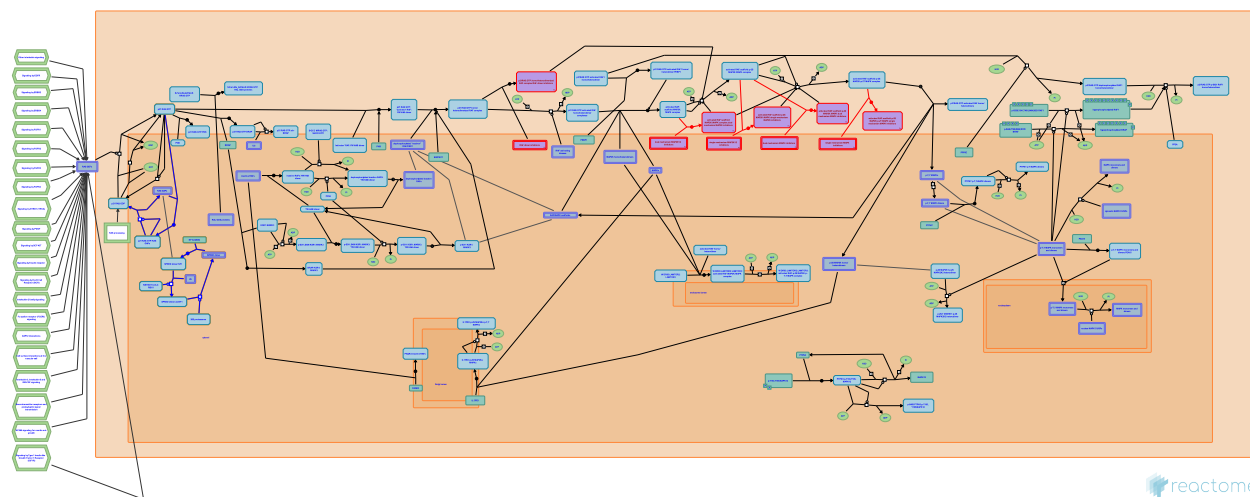


Regulation of RAS by GAPs



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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](https://reactome.org/textbook).

29/04/2024

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.

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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. [↗](#)

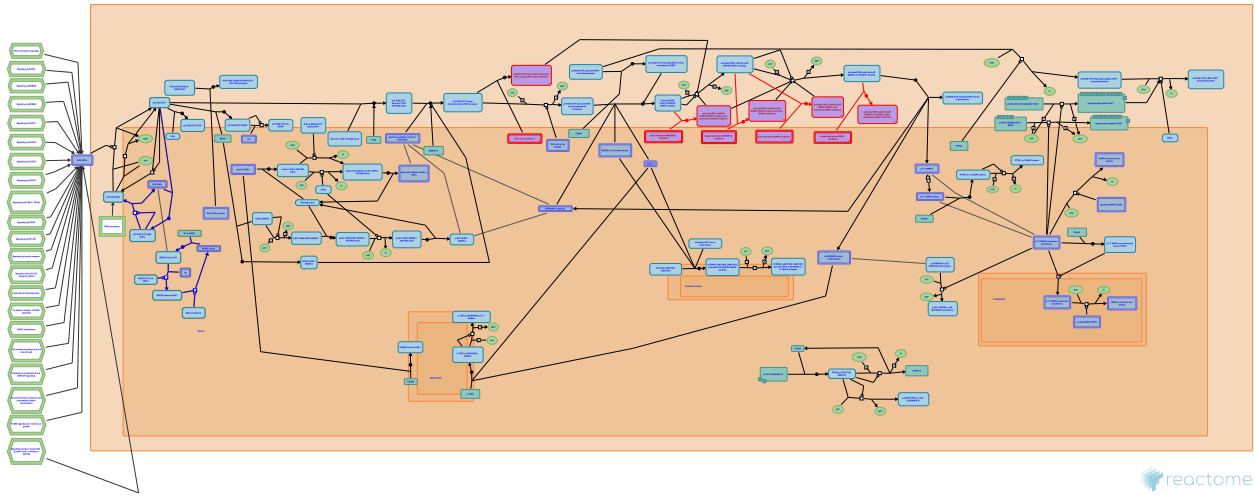
Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology*, 14, e1005968. [↗](#)

Reactome database release: 88

This document contains 1 pathway and 5 reactions ([see Table of Contents](#))

Regulation of RAS by GAPs ↗

Stable identifier: R-HSA-5658442



The intrinsic GTPase activity of RAS proteins is stimulated by the GAP proteins, of which there are at least 10 in the human genome (reviewed in King et al, 2013).

Literature references

Lapinski, PE., Lubeck, BA., King, PD. (2013). Nonredundant functions for Ras GTPase-activating proteins in tissue homeostasis. *Sci Signal*, 6, re1. ↗

Editions

2014-12-18	Authored	Rothfels, K.
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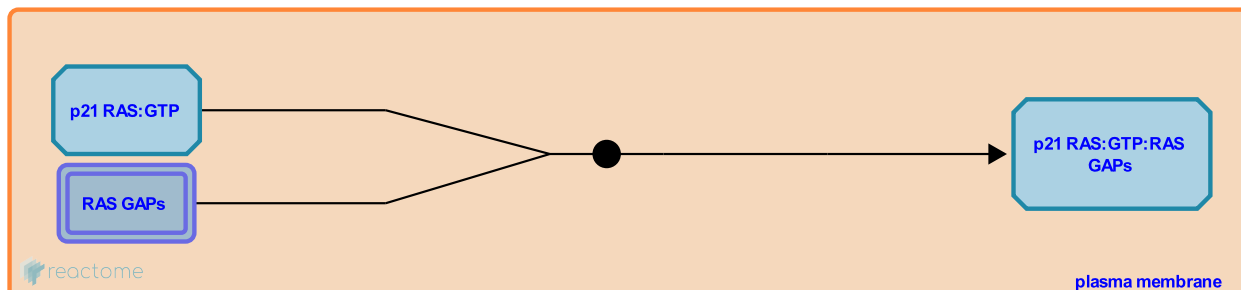
RAS GAPs bind RAS:GTP ↗

Location: [Regulation of RAS by GAPs](#)

Stable identifier: R-HSA-5658435

Type: binding

Compartments: plasma membrane



The human genome encodes at least 10 proteins that bind RAS and activate its intrinsic GTPase activity, resulting in the formation of inactive RAS:GDP and attenuating RAS signaling (reviewed in King et al, 2013). These identified RAS GAP proteins are RASA1 (also known as p120 GAP), NF1, the GAP1 family (RASA2, RASA3, RASA4 and RASAL1) and the SYNGAP family (SYNGAP1, DAB2IP, RASAL2 and RASAL3). GAP proteins stimulate RAS GTPase activity by inserting a conserved arginine residue into the RAS active site, promoting a conformational change in the active site to allow GTP hydrolysis (Ahamdian et al, 2003; Scheffzek et al, 1997; Ahamdian et al, 1997). In addition to the GAP domain, most RAS GAP proteins also contain membrane targeting domains that facilitate interaction with the plasma membrane where RAS is tethered. In some cases, such as RASA3, membrane localization is constitutive, whereas in others, the GAP proteins are targeted to the membrane in response to cellular signaling. In addition to binding RAS, a number of GAP proteins also mediate other protein-protein interactions and act as scaffolds to integrate signaling; some GAPs are also known to bind and activate other small GTPases such as RAP (reviewed in King et al, 2013). Loss-of-functions mutations in RAS GAP proteins have been identified in a number of cancers (reviewed in Maertens and Cichowski, 2014).

Followed by: [RAS GAPs stimulate RAS GTPase activity](#)

Literature references

- Lapinski, PE., Lubeck, BA., King, PD. (2013). Nonredundant functions for Ras GTPase-activating proteins in tissue homeostasis. *Sci Signal*, 6, re1. ↗
- Scheffzek, K., Ahmadian, MR., Stege, P., Kiel, C. (2003). Structural fingerprints of the Ras-GTPase activating proteins neurofibromin and p120GAP. *J. Mol. Biol.*, 329, 699-710. ↗
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2016-02-07	Reviewed	Pires, IM.

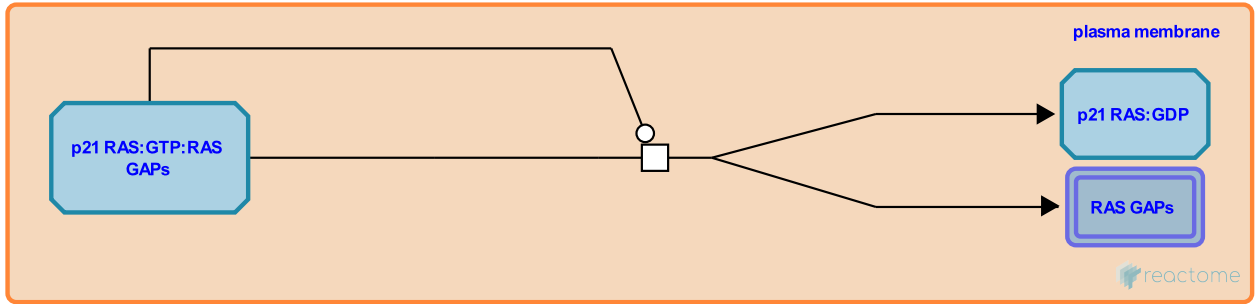
RAS GAPs stimulate RAS GTPase activity ↗

Location: [Regulation of RAS by GAPs](#)

Stable identifier: R-HSA-5658231

Type: transition

Compartments: plasma membrane



The intrinsic GTPase activity of RAS proteins is stimulated by the GAP proteins, of which there are at least 10 in the human genome (reviewed in King et al, 2013).

Preceded by: [RAS GAPs bind RAS:GTP](#)

Literature references

Lapinski, PE., Lubeck, BA., King, PD. (2013). Nonredundant functions for Ras GTPase-activating proteins in tissue homeostasis. *Sci Signal*, 6, re1. ↗

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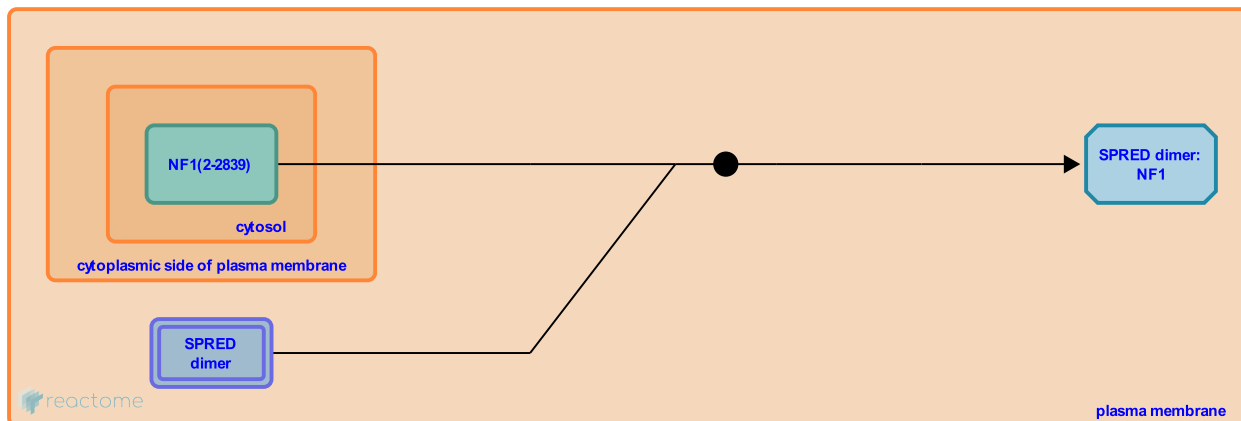
SPRED dimer binds NF1 ↗

Location: [Regulation of RAS by GAPs](#)

Stable identifier: R-HSA-5658438

Type: binding

Compartments: plasma membrane



Sprouty-related proteins (SPRED) 1, 2 and 3 are negative regulators of the MAPK pathway that act at least in part by recruiting the RAS GAP protein neurofibromin 1 (NF1) to the plasma membrane (Kato et al, 2003; King et al, 2006; Stowe et al, 2012). NF1, a negative regulator of RAS is a tumor suppressor that is mutated in the familial cancer syndrome neurofibromatosis I as well as in sporadic cases of glioblastoma, non-small cell lung cancers, neuroblastoma and melanoma (Martin et al, 1990; Bollag et al, 1996; reviewed in Bollag and McCormick, 1992; Maertens and Cichowski, 2014).

Plasma membrane-association of the SPRED proteins themselves depends on the C-terminal SPR domain. Mutations in this region abrogate membrane localization of the protein (King et al, 2005; Stowe et al, 2012). Membrane association may also be promoted by interaction of the SPRED proteins with RAS (Wakioka et al, 2001). Interaction with NF1 is mediated by the SPRED EVH1 domain, and mutations in this region affect both NF1 recruitment and the ability of SPRED and NF1 proteins to negatively regulate RAS pathway activity (Stowe et al, 2012; reviewed in McClatchey and Cichowski, 2012).

Followed by: [KBTBD7:CUL3:RBX1 ubiquitinates NF1](#)

Literature references

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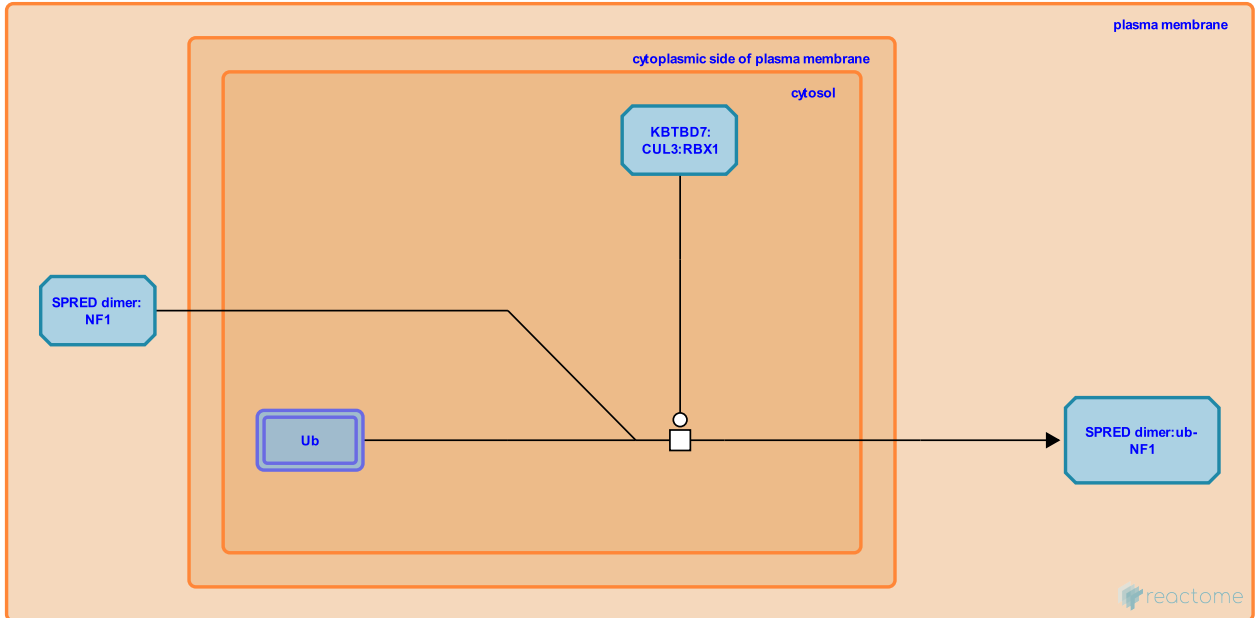
KBTBD7:CUL3:RBX1 ubiquitinates NF1 ↗

Location: [Regulation of RAS by GAPs](#)

Stable identifier: R-HSA-5658424

Type: transition

Compartments: cytosol



NF1 levels are controlled by proteasomal degradation in response to stimulation by some growth factors (Cichowski et al, 2003). Ubiquitination is mediated by the CUL3:RBX1 RING E3 ligase complex in conjunction with the BTB adaptor protein KBTBD7 (Hollstein et al, 2013). After its initial rapid degradation, NF1 protein levels are re-established shortly after growth factor treatment, allowing appropriate termination of RAS MAPK signaling (Cichowski et al, 2003). Aberrant destabilization of NF1 by CUL3:KBTBD7-mediated proteasomal degradation has been identified in cases of glioblastoma and depends on activation of PKC alpha (Cichowski et al, 2003; McGillicuddy et al, 2009; Hollstein et al, 2013).

Preceded by: [SPRED dimer binds NF1](#)

Followed by: [NF1 is degraded by the proteasome](#)

Literature references

Jacks, T., Jardim, M., Cichowski, K., Johnson, BW., Santiago, S. (2003). Dynamic regulation of the Ras pathway via proteolysis of the NF1 tumor suppressor. *Genes Dev.*, 17, 449-54. ↗

Cichowski, K., Hollstein, PE. (2013). Identifying the Ubiquitin Ligase complex that regulates the NF1 tumor suppressor and Ras. *Cancer Discov*, 3, 880-93. ↗

Stemmer-Rachamimov, AO., Moldenhauer, G., Fromm, JA., Liao, LM., Kubek, S., Cichowski, K. et al. (2009). Proteasomal and genetic inactivation of the NF1 tumor suppressor in gliomagenesis. *Cancer Cell*, 16, 44-54. ↗

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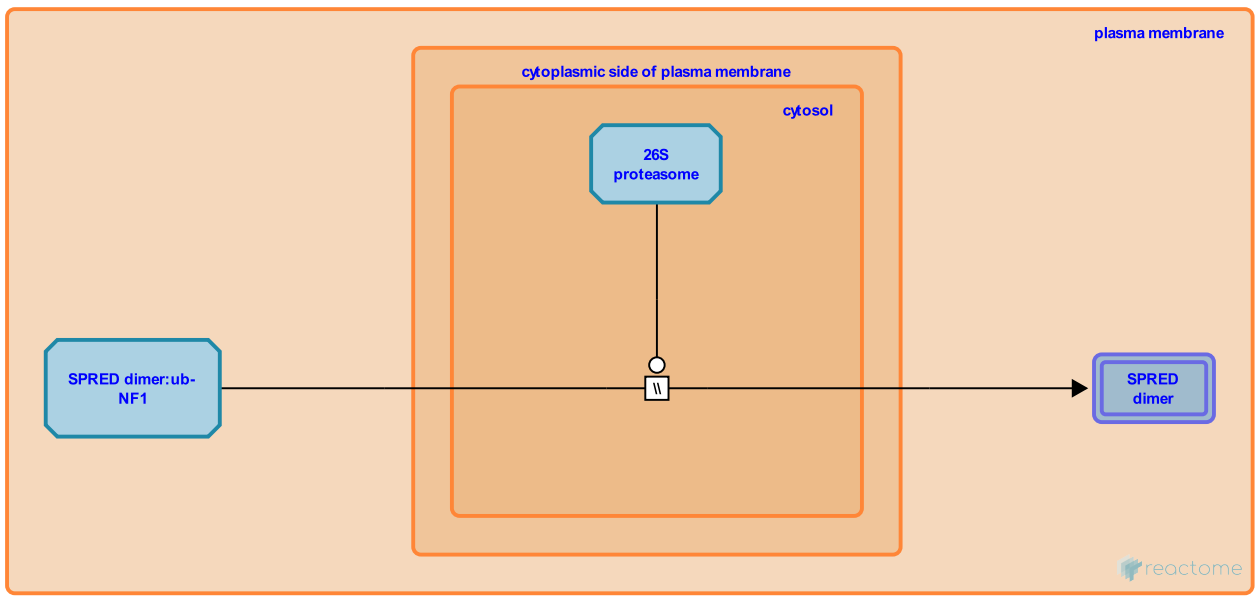
NF1 is degraded by the proteasome ↗

Location: [Regulation of RAS by GAPs](#)

Stable identifier: R-HSA-5658430

Type: omitted

Compartments: cytosol



After ubiquitination by the CUL3:KBTBD7 E3 RING ligase complex, NF1 is degraded by the proteasome (Cichowski et al, 2003; McGillicuddy et al, 2009; Hollstein et al, 2013).

Preceded by: [KBTBD7:CUL3:RBX1 ubiquitinates NF1](#)

Literature references

Jacks, T., Jardim, M., Cichowski, K., Johnson, BW., Santiago, S. (2003). Dynamic regulation of the Ras pathway via proteolysis of the NF1 tumor suppressor. *Genes Dev.*, 17, 449-54. ↗

Cichowski, K., Hollstein, PE. (2013). Identifying the Ubiquitin Ligase complex that regulates the NF1 tumor suppressor and Ras. *Cancer Discov.*, 3, 880-93. ↗

Stemmer-Rachamimov, AO., Moldenhauer, G., Fromm, JA., Liao, LM., Kubek, S., Cichowski, K. et al. (2009). Proteasomal and genetic inactivation of the NF1 tumor suppressor in gliomagenesis. *Cancer Cell*, 16, 44-54. ↗

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